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25 June, 2007

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TSCA Document Control Office (7407M)
ATTN: TSCA Section 8(e) Coordinator
EPA East Building, Room 6428
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20460-0001

8EHQ-07-16749

Re: TSCA 8(e) Supplemental Notice for 8EHQ-07-16749: Draft Final Sub-chronic Toxicity Data on 1,2-Diaminocyclohexane

Dear Sir:

INVISTA is submitting this letter to supplement its previous TSCA 8(e) submissions on February 28, 2007, April 2, 2007 and May 7. 2007 concerning draft results from an oral gavage OECD 422, sub-chronic toxicity study on 1,2-Diaminocyclohexane, CASRN 694-83-7, with additional draft toxicity data.

This draft final document (see attachment) summarizes the effects reported, to date, in this study. This 8(e) supplement will list additional findings, not yet reported to the Agency, which have just been made known to INVISTA by the testing Laboratory. These additional findings include:

1. Slight neurotoxicity was reported as slightly increased motor activity in 500 mg/kg females at the low sensor location.
2. Slight clinical biochemistry findings were noted as a treatment related decrease in eosinophils in males and females at 500 mg/kg. Also, cholesterol levels were increased, in males, at 150 mg/kg (earlier reported only at the 500 mg/kg dose, in males).
3. Microscopic examination of livers revealed slight hepatocellular vacuolization in males at 500 mg/kg. This finding supplements an earlier 8(e) submission regarding pale discoloration of livers, as well as previously submitted clinical biochemistry liver toxicity biomarkers.
4. Slight changes in lung and adrenal gland morphology were noted by macroscopic examination (lungs – grey-white foci in 500 mg/kg females) and by microscopic examination (lungs and adrenal glands at 500 mg/kg only) and were correlated with decreases in lung and adrenal organ weights. Slight microscopic changes included: A. A moderate increase was observed in incidence and severity of alveolar macrophage foci in lungs of 500 mg/kg females. B. Lymphocytic alveolar inflammation incidence was slightly increased in lungs of 500 mg/kg males and an increase in lymphocytic alveolar inflammation severity was observed in lungs of 500 mg/kg females. C. In 500 mg/kg males, minor vacuolization in the zona fasiculata of the adrenal glands was observed as a possible treatment related trend.
5. There was an increased incidence in missing or cannibalized pups in all treatment groups when compared to concurrent or historical controls. No dose response relationship was apparent but this finding may be treatment related. This increased incidence correlated with an increase in post natal loss which was observed at 50 mg/kg (previously reported at 150 and 500 mg/kg).

These findings do not necessarily indicate that 1,2-Diaminocyclohexane is a specific neurological, reproductive, or developmental toxicant. Although maternal toxicity is apparent at the high dose, and

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likely at the mid dose, EPA guidelines generally require reporting of neurological, reproductive, or developmental effects at any dose regardless of the presence of maternal toxicity.
The above information is from a draft study that has not yet been completed. INVISTA will submit the final version of the study to EPA when it becomes available.

This report is being submitted in accordance with TSCA Section 8(e) guidance. Please do not hesitate to contact me if you have any questions. I may be reached at (316) 828-1470.

Sincerely,

Betsy Duncan

Betsy Duncan
TSCA Program Manager
Environmental Health and Safety

Attachment

DRAFT REPORT APPROVAL STATEMENT

Study Title	A combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test of DYTEK® DCH-99 in rats by oral gavage.
NOTOX Substance	170676/A
NOTOX Project	479003

STUDY DIRECTOR STATEMENT

The undersigned declares that this draft report constitutes a true account of the procedures adopted and the results obtained in the performance of this study.

Study director

.....
Ir. M.H.M. van Tuyl

04 June 2007
date:

APPROVAL
Management

.....
Drs. A.W.M. van Rozendaal

04 June 2007
date:

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DRAFT REPORT

Version 1

Study Title

A COMBINED 28-DAY REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST OF DYTEK® DCH-99 IN RATS BY ORAL GAVAGE

Author

Ir. M.H.M. van Tuyl

Study completion date

\

Test Facility

NOTOX B.V.
Hambakenwetering 7
5231 DD 's-Hertogenbosch
The Netherlands

Laboratory Study Identification

NOTOX Project 479003
NOTOX Substance 170676/A

1. CONTENTS

2. STATEMENT OF GLP COMPLIANCE

NOTOX B.V., 's-Hertogenbosch, The Netherlands

The study described in this report has been correctly reported and was conducted in compliance with:

The Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice Guidelines (1997).

Which essentially conform to:

The United States Food and Drug Administration Good Laboratory Practice Regulations.

The United States Environmental Protection Agency Good Laboratory Practice Regulations.

The sponsor is responsible for Good Laboratory Practice (GLP) compliance for all test substance information unless determined by NOTOX.

The GLP statement for the delegated phase histopathology is included in Appendix 4 of this report.

NOTOX B.V.

Ir. M.H.M. van Tuyl
Study Director

Drs. A.W.M. van Rozendaal
Section Head Toxicology

Date: .....

Date: .....

3. LEAD QUALITY ASSURANCE STATEMENT

NOTOX B.V., 's-Hertogenbosch, The Netherlands

This report was inspected by the NOTOX Quality Assurance Unit to confirm that the methods and results accurately and completely reflect the raw data.

The dates of Quality Assurance inspections are given below.
During the on-site process inspections procedures applicable to this type of study were inspected.

The reporting date is the date of reporting to the Study Director. The QAU report was then forwarded to the Test Facility Management.

Type of inspections	**Phase / Section**	**Start Inspection date(s)**	**End Inspection date(s)**	**Reporting date**
Protocol (Study)		DD\MMM\JJ	DD\MMM\JJ	DD\MMM\JJ
On-site (Process)		DD\MMM\JJ	DD\MMM\JJ	DD\MMM\JJ
On-site (Study)		DD\MMM\JJ	DD\MMM\JJ	DD\MMM\JJ
Report (Study)		DD\MMM\JJ	DD\MMM\JJ	DD\MMM\JJ

The Quality Assurance programme for the delegated phase histopathology was performed by the Quality Assurance appointed by the test site management and a Quality Assurance statement is included in Appendix 4 of this report.

Head of Quality Assurance
C.J. Mitchell B.Sc.

Date: .....

4. SUMMARY

Combined repeated dose toxicity study with reproduction / developmental toxicity screening test with Dytek® DCH-99 administered by oral gavage in Wistar rats.

The purpose of this study was to evaluate the potential toxic effects of Dytek® DCH-99 when administered to rats for a minimum of 28 days and to evaluate the potential of the test substance to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development.

The study was based on the following guideline:
Organisation of Economic Co-operation and Development Guidelines (OECD) for testing of Chemicals Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, March 1996.

After acclimatisation, four groups of ten male and ten female Wistar rats were exposed by oral gavage to the test substance at 0, 50, 150 and 500 mg/kg/day.
Males were exposed for 31 days, i.e. 2 weeks prior to mating, during mating, and up to termination. Females were exposed for 42 to 45 days, i.e. during 2 weeks prior to mating, during mating, during *post-coitum*, and during at least 3 days of lactation.

The following parameters were evaluated: clinical signs, functional observations, body weights, food consumption, reproduction processes, observations offspring, clinical pathology, macroscopy, organ weights, and histopathology. Chemical analyses of formulations were conducted once during the study to assess accuracy, homogeneity and stability.

RESULTS

Accuracy, homogeneity and stability of formulations were demonstrated by analyses.

Parental toxicity
No treatment related mortality occurred during the study period.

Slight to moderate salivation was noted in all males and females treated at 500 mg/kg. Furthermore, incidentally rales were noted in two males at 500 mg/kg and piloerection was noted in one female at 500 mg/kg at the end of treatment.

At 500 mg/kg, reduced body weight gain was noted in males during the treatment period and in females on Days 14 to 20 *post-coitum* and during lactation (not always statistically significant). Furthermore, at 500 mg/kg food consumption before or after allowance for body weight was reduced during lactation in females (statistically not significant).

Hearing ability, pupillary reflex, static righting reflex and grip strength were normal in all animals. The motor activity test showed an increase in activity at the low sensor for females at 500 mg/kg, which might be due to hyperactivity of the dam and/or pups.

At 500 mg/kg, a treatment related decrease in eosinophils was noted in males and females. Furthermore, treatment related effects were noted in clinical biochemistry (mainly in males). These findings comprised high alanine aminotransferase, aspartate aminotransferase activities (also noted in females at 500 mg/kg) and alkaline phosphatase activities and high cholesterol levels. Cholesterol levels were also increased in males treated at 150 mg/kg, but to a lesser extent. These findings at 500 mg/kg correlated with the macroscopic or microscopic effects on the liver, e.g. pale discolouration, increased liver/body weight ratios and hepatocellular vacuolation of the liver at a minimal or slight degree. In addition, calcium levels were increased in males and females at 500 mg/kg.

Besides microscopic changes in the liver, minor morphological alterations were noted in the lungs and adrenal glands:

- In the lungs, alveolar macrophage foci were increased in incidence and severity to moderate in females at 500 mg/kg. In the same organ lymphocytic alveolar inflammation was slightly increased in incidence in males and in incidence and severity to moderate in females. These findings correlated with the grey-white foci observed in females at 500 mg/kg.
- In the adrenal glands of males vacuolation in the zona fasiculata at minor degrees of severity was slightly increased in incidence at 500 mg/kg which was not statistically significant. However there was a positive trend.

The findings in liver, lung and adrenal glands were chiefly minor in nature and may be regarded as either slight increases in spontaneously occurring conditions or adaptive. As such they were considered to be indicators of slight toxicity to the test-item.

The organ weight changes in thymus and kidney correlated with the microscopic findings in these organs, e.g. atrophy and basophilia respectively. No corroborative findings were noted for the changes in weight of the heart, epididymides and brain. These changes were mild in nature and in absence of corroborative findings or a clear dose response relationship, the toxicological relevance of these changes remains unclear.

Reproductive toxicity

The gestation index was decreased in females at 500 mg/kg. No effect was noted on the duration of gestation and precoital time at 50, 150 or 500 mg/kg.

Of all animals, three females did not mate (one in the control group, one in the low dose group and one in the high dose group) and two females had implantations sites only (high dose group).

In males suspected of infertility, there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. Further, the spermatogenic staging profiles were normal for all Group 1 and Group 4 males evaluated.

In females suspected of infertility, animal 75 (group 4) had endometrial inflammation. Animals 73 and 77 (group 4) had vaginal epithelial mucification (possible oestrus cycle disturbance).

Breeding toxicity

At 500 mg/kg, the average and total number of living pups per litter was reduced at the first litter check, (average of 6.9 pups per litter) when compared to concurrent controls (average of 16.0 pups per litter).

An increased incidence in postnatal loss was noted at 50, 150 and 500 mg/kg, resulting in a reduced viability index. No dose response relationship could be established between the treated groups.

Developmental toxicity

There was an increased incidence in missing and cannibalized pups, correlating with the increased post natal loss noted at 50, 150 and 500 mg/kg when compared to the concurrent controls.

In surviving pups no treatment related changes in developmental indices were noted. Furthermore, (mean) body weights were similar for the control and treated groups.

CONCLUSION

In conclusion, treatment with Dytek® DCH-99 by oral gavage in male and female Wistar rats at dose levels of 0, 50, 150 and 500 mg/kg/day revealed parental and reproduction toxicity at 500 mg/kg body weight/day. Breeding and developmental toxicity, e.g. increased incidence of postnatal loss, cannibalism and/or missing pups was observed at all treated groups. Although no dose response relationship could be established, the observed increase was considered to be related to treatment as no such increased incidence was noted in concurrent and historical control data.

Based on these findings, the parental and reproduction No Observed Adverse Effect Level (NOAEL) was established at 150 mg/kg body weight/day. No breeding NOAEL could be established.

Based on results in surviving pups, the developmental NOAEL was established at 500 mg/kg. However, the cause of the observed cannibalism was unclear and might be related to developmental effects, which will then affect the NOAEL.

5. INTRODUCTION

5.1. Preface

This is a multi-site study. The study was performed according to the OECD Consensus document Number 13 *The Application of the OECD Principles of GLP to the Organization and Management of Multi-Site studies.*

Information concerning the delegated phase is given in the applicable appendice.

Phase:	Histopathology (see Appendix 4)
Sponsor	INVISTA S.à.r.l. 4123 East 37th Street North, WICHITA, KS 67220 USA
Study Monitor	Mr. J.D. Jernigan, Ph.D. (until 18 December 2006) Mrs. H.J. Blankinship (from 18 December 2006 onwards)
Study Director	M.E.W. Beekhuijzen, M.Sc. (until 14 December 2006) Ir. M.H.M. van Tuyl (from 14 December onwards) NOTOX B.V. Hambakenwetering 7 's-Hertogenbosch The Netherlands Tel: +31.73 640 6700 Fax: +31.73 640 6799 Email: Miranda.van.tuyl@notox.nl
Coordinating Biotechnician	C. Dohmen (NOTOX B.V.)
Clinical Pathology	J.E. van Kesteren (NOTOX B.V.)
Principal Scientist Analytical Chemistry	Dr. Ir. E. Baltussen (NOTOX B.V.)
Histotechnology	Ing T.A. Mijnders (NOTOX B.V.)
Necropsy	J.H. van den Brink, DVM (NOTOX B.V.)
Lead QA	C.J. Mitchell, B.Sc. (NOTOX B.V.): christine.mitchell@notox.nl
Test facility Management	W.J.A.M. Frieling DVM (NOTOX B.V.): wilbert.frieling@notox.nl
Test Facility	NOTOX B.V. Hambakenwetering 7 5231 DD 's-Hertogenbosch The Netherlands

5.2. Study schedule

Delivery of animals	03 January 2007
Experimental start date	03 January 2007 (allocation)
Start treatment	08 January 2007
Start mating	22 January 2007
Necropsy of males	08 February 2007
Delivery of litters	14, 15, 16, 17 and 18 February 2007
Necropsy of females and pups	19, 20, 21 and 22 February 2007
Experimental completion date	22 February 2007 (end in-life)

5.3. Project numbers

Two project numbers were used to collect online data. Eventually, all data was reported under NOTOX Project 479003.

Project number	Online data
481049	Parental animals: Clinical signs Functional observations Body weights and food consumption pre-mating Body weights post-mating/mating period males Clinical laboratory investigations Macroscopic findings and organ weights
479003	All other data

5.4. Aims of study

The purpose of this study was to evaluate the potential toxic effects of the test substance when administered to rats for a minimum of 28 days and to evaluate the potential of the test substance to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development.

This study should provide part of a rational basis for toxicological risk assessment in man.

5.5. Guidelines

This protocol was reviewed and agreed by the Laboratory Animal Welfare Officer and the Ethical Committee of NOTOX (DEC NOTOX 06-104) as required by the Dutch Act on Animal Experimentation (February 1997).

The study procedures described in this protocol were based on the following guideline:

1) Organisation of Economic Co-operation and Development Guidelines (OECD) for testing of Chemicals Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, March 1996.

5.6. Storage and retention of records and materials

Records and materials pertaining to the study, including protocol, raw data, specimens (except specimens requiring refrigeration or freezing) and the final report, will be retained in the NOTOX archives for a period of at least 10 years after finalization of the report. After this period, the sponsor will be contacted to determine whether raw data and specimens should be returned to them, retained or destroyed on their behalf.

Those specimens requiring refrigeration or freezing will be retained by NOTOX for as long as the quality of the specimens permits evaluation but no longer than three months after finalization of the report.

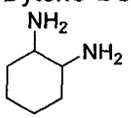
NOTOX will retain a test substance sample until the expiry date, but no longer than 10 years after finalization of the report. After this period the sample will be destroyed.

Storage and retention of records and materials by the test sites for the delegated phases are described in the applicable appendices.

6. MATERIALS AND METHODS

6.1. Test substance

6.1.1. Test substance information (170676/A)

Identification	Dytek® DCH-99
Structure	
Molecular formula	$C_6H_{14}N_2$
Molecular weight	114.19
Description	Clear light-yellow liquid
Batch	VS52185886
Composition	99.55% 1,2-Diaminocyclohexane (CAS 694-83-7) 0.24% 2-Aminomethylcyclopentylamine (CAS 21544-02-5) 0.08% Hexamethyleneimine (CAS 111-49-9) 0.00% Hexamethylenediamine (CAS 124-09-4) 0.07% 2-Methyl-1,5-pentamethylenediamine (CAS 15520-10-2) 0.06% Water
Test substance storage	At room temperature in the dark under nitrogen
Stability under storage conditions	Stable
Expiry date	02 October 2007

6.1.2. Study specific test substance information

Specific Gravity	0.94
Solubility in vehicle (Water)	Miscible

6.1.3. Test substance formulation

Vehicle	Water (Milli-U) (Millipore Corporation, Bedford, USA)
Rationale for vehicle	Based on trial formulations performed at NOTOX.
Stability of test substance in vehicle	Stable for at least 5 hours when stored at room temperature (See Appendix 3)
Method of formulation	Formulations (w/w) were prepared daily within 4 hours prior to dosing and were homogenised to a visually acceptable level. Adjustment was made for specific gravity of the test substance.
Storage conditions	At ambient temperature.

6.1.4. Chemical analysis of dose preparations

Analyses were done according to validated method (NOTOX Project 479025) on the samples used on 08 January 2007 as specified below.

Group	Analysis (type of sample)
1	acc (M)
2	acc + hom + $stab_{t=0}$ (TMB), $stab_{t=5, RT}$ (S)
3	acc (M)
4	acc + hom + $stab_{t=0}$ (TMB), $stab_{t=5, RT}$ (S)

Duplicate samples were analysed
acc=accuracy, hom=homogeneity, stab=stability (hours), T=top, M=middle, B=bottom position of container
S=stability sample taken at middle position of container
RT=room temperature

6.2. Test system

Test System	Rat: male and female Wistar rats Crl: (WI) BR (outbred, SPF-Quality). Untreated animals and virgin females were used at initiation of the study.
Rationale	This species and strain of rat has been recognized as appropriate for general and reproductive toxicity studies. NOTOX BV has general and reproductive historical data in this species from the same strain and source. This animal model has been proven to be susceptible to the effects of reproductive toxicants.
Source	Charles River Deutschland, Sulzfeld, Germany.
Age at start F_0-treatment	Approximately 10 weeks.
Number of F_0-animals	40 females and 40 males.
Acclimatisation F_0	At least 5 days prior to start of treatment.
Health check F_0	A health inspection was performed prior to commencement of treatment to ensure that the animals were in a good state of health.
Randomisation F_0	Prior to commencement of treatment, by computer-generated random algorithm according to body weight, with all animals within ± 20% of the sex mean.
Identification F_0	Earmark and tattoo.

Breeding procedures

Following a minimum of 14 days of exposure for the males and females, one female was cohabitated with one male of the same treatment group, avoiding sibling mating (Charles River supplied non-litter mates). Detection of mating was confirmed by evidence of sperm in the vaginal lavage or by the appearance of an intravaginal copulatory plug. This day was designated Day 0 *post-coitum*. Once mating has occurred, the males and females were separated.
The following females showed no evidence of mating after 14 days of mating: Females 43, 45 and 50 (Group 1), 51, 55 and 59 (Group 2) and females 73 and 79 (Group 4). These females were separated from their males after 14 days, but were placed back with the same males on Day 15 of mating until mating was detected. Mating continued until the day of necropsy of the males (Day 18 of mating). Females who showed no evidence of mating on the day before necropsy of the males, remained with their males overnight, and were kept without food.

Parturition F_0

The females were allowed to litter normally. Day 1 of lactation was defined as the day when a litter was found completed (i.e. membranes, placentas cleaned up, nest build up and/or feeding of pups started). Females that were littering were left undisturbed.

Lactation F_0

Deficiencies in maternal care, such as inadequate construction or cleaning of the nest, pups left scattered and cold, physical abuse of pups or apparently inadequate lactation or feeding, were recorded.

Identification offspring

The offspring was individually identified by means of intracutaneous injection of Indian ink.

6.3. Allocation

Group	Dose level mg/kg b.w./day	Number of animals		Animals numbers	
		F_0 males	F_0 females	males	females
1	0	10	10	01-10	41-50
2	50	10	10	11-20	51-60
3	150	10	10	21-30	61-70
4	500	10	10	31-40	71-80

* Dose levels following were based on a dose range finding study (see Appendix 5).

6.4. Animal husbandry

Animals were housed in Room 16.

Conditions
Animals were housed in a controlled environment, in which optimal conditions were considered to be approximately 15 air changes per hour, a temperature of 21 ± 3°C (actual range: 21.0 – 22.7°C), a relative humidity of 30 – 70% (actual range: 42 - 60%) and 12 hours artificial light and 12 hours darkness per day (nightlight during the night period).

Accommodation

Pre-mating	Animals were housed in groups of 5 animals/sex/cage in Macrolon cages (MIV type, height 18 cm).
Mating	Females were caged together with males on a one-to-one-basis in Macrolon cages (MIII type, height 18 cm).
Post-mating	Males were housed in groups of 5 animals/sex/cage in Macrolon cages (MIV type, height 18 cm). Females will be individually housed in Macrolon cages (MIII type, height 18 cm).
Lactation	Offspring was kept with the dam until termination.
General	Sterilised sawdust as bedding material (Litalabo, S.P.P.S., Argenteuil, France) and paper as cage-enrichment (Enviro-dri, Wm. Lillico & Son (Wonham Mill Ltd), Surrey, United Kingdom) were supplied. Certificates of analysis were examined and then retained in the NOTOX archives. During overnight activity monitoring, animals were housed individually in Macrolon cages (MIII type; height 15 cm) with sterilised sawdust as bedding material. No cage-enrichment was provided during overnight activity monitoring.

Diet
Free access to pelleted rodent diet (SM R/M-Z from SSNIFF® Spezialdiäten GmbH, Soest, Germany). Each batch was analysed for nutrients and contaminants are analysed on a regular basis. Results were examined and archived.

Water
Free access to tap-water. Certificates of analysis (performed quarterly) were examined and archived.

Analysis of bedding, paper, diet and water did not reveal any findings that were considered to have affected study integrity.

6.5. Treatment

6.5.1. Parental animals

Method	Plastic feeding tube.
Frequency	Once daily for 7 days per week, approximately the same time each day with a maximum of 4 hours difference between the earliest and latest dose. Animals were dosed up to the day prior to scheduled necropsy.
Exposure period	The males and females were exposed for at least 14 days prior to mating, during mating, and up to the day prior to necropsy. Exposure period was at least until the minimum total dosing period of 28 days was completed.
Dose volume	20 ml/kg body weight. Actual dose volumes were calculated according to the latest body weight.

6.5.2. Offspring

Offspring was not treated.

6.6. Observations

6.6.1. Parental animals

The following animals were selected by the study director for functional observations, clinical laboratory investigations, macroscopic examination and determination of organ weights.

Group	Animals numbers									
	Males (n=5)					Females (n=5)				
1	1	2	4	6	7	42	44	45	47	48
2	12	13	14	16	17	52	53	54	58	59
3	21	22	23	24	25	62	63	64	66	70
4	31	32	34	35	36	71	72	74	78	80

Mortality / Viability

At least twice daily.

Clinical signs

At least once daily, detailed clinical observations were made in all animals. Once prior to start of treatment and at weekly intervals this was also performed outside the home cage in a standard arena. Arena observations were not performed when the animals were mating, or housed individually. The time of onset, degree and duration was recorded. All symptoms were recorded and graded according to fixed scales:
Maximum grade 1: grade 0 = absent, grade 1 = present
Maximum grade 3 or 4: grade 1 = slight, grade 2 = moderate, grade 3 = severe, grade 4 = very severe
Cage debris of pregnant females was examined to detect abortion or premature birth, if applicable. Signs of difficult or prolonged parturition were recorded, if applicable.

Functional Observations

The following tests were performed in 5 males and 5 females, randomly selected from each group:

- hearing ability, pupillary reflex, static righting reflex and grip strength (Score 0 = normal/present, score 1 = abnormal/absent).
- motor activity test (recording period: 12 hours during overnight for individual animals, using a computerised monitoring system, Pearson Technical Services, Debenham, Stowmarket, England).

During the motor activity test, males were caged individually and females were caged with their offspring.

The assigned males were tested during week 4 of treatment and the assigned females were tested during lactation (all before blood sampling).

In order to avoid hypothermia of pups, dams were removed from the pups for not more than 30-40 minutes.

Body weights	Males and females were weighed on the first day of exposure and weekly thereafter. Mated females were weighed on Days 0, 4, 7, 11, 14, 17 and 20 *post-coitum*, and on Days 1 and 4 of lactation.
Food consumption	Weekly, for males and females. Food consumption was not recorded during the breeding period. Food consumption of mated females was measured on Days 0, 4, 7, 11, 14, 17 and 20 *post-coitum* and after delivery on Days 1 and 4 of lactation.
Water consumption	Subjective appraisal was maintained during the study, but no quantitative investigation introduced as no effect was suspected.
Reproduction processes	Male number paired with, mating date, confirmation of pregnancy, and delivery day was recorded.

6.6.2. Offspring

Each litter was examined to determine the following, if practically possible:

Mortality / Viability	The numbers of live and dead pups at the First Litter Check (= check at Day 1 of lactation) and daily thereafter were determined. If possible, defects or cause of death were evaluated. Animals showing pain, distress or discomfort, which is considered not transient in nature or is likely to become more severe, were sacrificed for humane reasons based on OECD guidance document on humane endpoints (ENV/JM/MONO/ 2000/7).
Clinical signs	At least once daily, detailed clinical observations were made in all animals.
Body weights	Live pups were weighed on Days 1 and 4 of lactation.
Sex	Was determined for of all pups on Days 1 and 4 of lactation (by assessment of the ano-genital distance).

6.7. Clinical laboratory investigations

Blood samples were collected from 5 males and 5 females randomly selected from each group under iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) anaesthesia immediately prior to scheduled *post mortem* examination, between 7.00 and 10.30 a.m. The animals were fasted overnight (with a maximum of 20 hours) before blood sampling, but water was provided. Blood samples were drawn from the retro-orbital sinus and collected into tubes (Greiner Bio-One, Bad Haller, Austria) prepared with EDTA for haematological parameters (0.5 ml), with citrate for clotting tests (0.9 ml) and Li-heparin treated tubes for clinical biochemistry parameters (0.5 ml). The following parameters were determined:

Parameter	Abbreviation	Unit
Haematology [a]		
White blood cells	WBC	10^9/l
Differential leucocyte count neutrophils, lymphocytes, monocytes, eosinophils, basophils		%WBC
Red blood cells		10^{12}/l
Reticulocytes		%RBC
Red blood cell distribution width	RDW	%
Haemoglobin		mmol/l
Haematocrit		l/l
Mean corpuscular volume	MCV	fl
Mean corpuscular haemoglobin	MCH	fmol
Mean corpuscular haemoglobin concentration	MCHC	mmol/l
Platelets		10^9/l
Clotting Potential [b]		
Prothrombin time	PT	s
Activated Partial thromboplastin time	APTT	s
Clinical Biochemistry [c]		
Alanine aminotransferase	ALAT	U/l
Aspartate aminotransferase	ASAT	U/l
Alkaline phosphatase	ALP	U/l
Total Protein		g/l
Albumin		g/l
Total Bilirubin		µmol/l
Urea		mmol/l
Creatinine		µmol/l
Glucose		mmol/l
Cholesterol		mmol/l
Sodium		mmol/l
Potassium		mmol/l
Chloride		mmol/l
Calcium		mmol/l
Inorganic Phosphate	Inorg. Phos	mmol/l

[a] Instrumentation: ADVIA 120 (Bayer Diagnostics).

[b] Instrumentation: STA Compact (Roche Diagnostics).

[c] Instrumentation: Olympus AU400 (Goffin Meyvis).

6.8. Pathology Parental Animals

6.8.1. Termination

All animals were fasted overnight (with a maximum of 20 hours) prior to planned necropsy, but water was provided.

Females Which Deliver
On lactation Day 5 or shortly thereafter, the F_0-females were anaesthetised using iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated. Organ weights were collected and tissues were preserved for possible future histopathological examination as described in the following paragraphs. The number of former implantation sites were counted and recorded. Corpora lutea were also counted and recorded. Gross lesions were saved for possible future histopathological examination.

Females Which Fail to Deliver
On post-mating Day 24-26 (females with evidence of mating) or post-cohabitation Day 24-26 (females without evidence of mating), the F_0- females which had not delivered were anaesthetised using iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated. Organ weights were collected and tissues were preserved for possible future histopathological examination as described in the following paragraphs, with the following exceptions: Nongravid uteri were opened and placed in 10% ammonium sulfide solution as described by Salewski (Salewski, 1964) for the detection of implantation sites. If evidence of macroscopic implantations was present, the number of implantation sites and corpora lutea was recorded. Gross lesions were saved for possible future histopathological examination.

Females with Total Litter Loss
Females with total litter loss were anaesthetised using iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated within 24 hours of litter loss. Tissues were preserved for possible future histopathological examination as described in the following paragraphs. The number of former implantation sites and corpora lutea were recorded. Gross lesions were saved for possible future histopathological examination.

F_0-Deaths and Animals Euthanized in Extremis
Females not surviving until the scheduled euthanasia were necropsied as described in the following paragraphs. Animals not expected to survive to the next observation period (moribund) were anaesthetised using iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated. Organ weights were not collected. Tissues were preserved for possible future histopathological examination as described in the following paragraphs with the following exceptions: The number and location of implantation sites or scars was recorded. Corpora lutea (for animals dying or euthanized during gestation) was also counted and recorded. Recognizable fetuses were examined externally, euthanized by decapitation (if necessary) and preserved in 10% neutral-buffered formalin.

Termination Procedures for F_0-Males
Following completion of the mating period (a minimum of 28 days of dose administration), the F_0-males were anaesthetised using iso-flurane (Abbott Laboratories Ltd., Zwolle, The Netherlands) and subsequently exsanguinated. Organ weights were collected and tissues were preserved for possible future histopathological examination as described in the following paragraphs.

6.8.2. Macroscopic examination

After sacrifice or death all parental animals were subjected to macroscopic examination of the cranial, thoracic and abdominal tissues and organs, with special attention being paid to the reproductive organs. Descriptions of all macroscopic abnormalities was recorded.

Samples of the following tissues and organs were collected and fixed in neutral phosphate buffered 4% formaldehyde solution (Klinipath, Duiven, The Netherlands):

From 5 selected animals/sex/group:

Identification marks: not processed
Adrenal glands
Aorta
Brain (cerebellum, mid-brain, cortex)
Caecum
Cervix
Clitoral gland
Colon
Coagulation gland
Duodenum
Epididymides*
(Eyes* with optic nerve (if detectable) and Harderian gland)
(Female mammary gland area)
(Femur including joint)
Heart
Ileum
Jejunum
Kidneys
(Larynx)
(Lacrimal gland, exorbital)
Liver
Lung, infused with formalin
Lymph nodes - mandibular, mesenteric
(Nasopharynx)
Oesophagus
Ovaries
Pancreas
Peyer's patches (jejunum, ileum) if detectable
Pituitary gland
Preputial gland
Prostate gland
Rectum
(Salivary glands - mandibular, sublingual)
Sciatic nerve
Seminal vesicles
(Skeletal muscle)
(Skin)
Spinal cord -cervical, midthoracic, lumbar
Spleen
Sternum with bone marrow
Stomach
Testes*
Thymus
Thyroid including parathyroid (if detectable)
(Tongue)
Trachea
Urinary bladder
Uterus
Vagina
All gross lesions

From all remaining animals:

Cervix
Clitoral gland
Coagulation gland
Epididymides*
Ovaries
Preputial gland
Prostate gland
Seminal vesicles
Testes*
Uterus
Vagina
All gross lesions

* Fixed in modified Davidson's solution (prepared at NOTOX using Formaldehyde 37-40%, Ethanol, Acetic acid (glacial)(all Merck, Darmstadt, Germany) and Milli-Ro water (Millipore Corporation, Bedford, USA)) and transferred to formalin after fixation for at least 24 hours.
Tissues/organs mentioned in parentheses were not examined by the pathologist, since no signs of toxicity were noted at macroscopic examination.

6.8.3. Organ weights

The following organ weights (and terminal body weight) was recorded:

From 5 selected animals/sex/group

Adrenal glands	Liver
Brain	Spleen
Epididymides	Testes
Heart	Thymus
Kidneys	

From all remaining males:

Epididymides
Testes

6.8.4. Histotechnology

All organ and tissue samples, as defined under Histopathology (following), were processed, embedded and cut at a thickness of 2-4 micrometers and stained with haematoxylin and eosin (Klinipath, Duiven, The Netherlands).
Of the selected 5 males/group of the control and high dose group, additional slides of the testes were prepared to examine staging of spermatogenesis. The testes was processed, sectioned at 3-4 microns, and stained with PAS/haematoxylin.

6.8.5. Histopathology

The following slides were examined by a pathologist:
- The preserved organs and tissues of the selected animals of Groups 1 and 4.
- The additional slides of the testes of the selected 5 males/group of Groups 1 and 4 to examine staging of spermatogenesis
- all gross lesions of all animals (all dose groups)
- The reproductive organs (cervix, coagulation gland, epididymis, ovaries, prostate gland, seminal vesicles, testis, uterus, and vagina) of all animals suspected of infertility (e.g. those that failed to mate, conceive, sire or deliver healthy offspring). These animals include:
    - Group 1: Male 10 and Female 50.
    - Group 2: Males 11, 15 and 20 and Females 51, 55 and 60.
    - Group 4: Males 33, 35, 37 and 39 and Females 73, 75, 77 and 79.

On detection of possible treatment-related changes in the organs of any animal in the high dose group, histological examination was extended to lungs, thymus, liver, kidneys (all males and females) and adrenals (males only) of five selected animals of Groups 2 and 3.

All abnormalities were described and included in the report. An attempt was made to correlate gross observations with microscopic findings.

For further details, see Appendix 4.

6.9. Pathology Offspring

6.9.1. Termination

Pups were killed by decapitation on Day 4 of lactation or shortly thereafter.

6.9.2. Macroscopic examination

All offspring was sexed and externally examined if practically possible. The stomach was examined for the presence of milk. Descriptions of all macroscopic abnormalities was recorded. If possible, defects or cause of death were evaluated. Any abnormal pup, organ or tissue was preserved in neutral phosphate buffered 4% formaldehyde solution, for possible further examination.

6.10. Calculations

For each dose group reproduction parameters were expressed in two ways:
- As a mean (with standard deviation) of the number observed for each litter
- Relative to a second parameter and calculated on a total group basis

For each group the following calculations were performed:

Percentage mating	$\frac{\text{Number of females mated}}{\text{Number of females paired}} \times 100$
Fertility index	$\frac{\text{Number of pregnant females}}{\text{Number of females paired}} \times 100$
Conception rate	$\frac{\text{Number of pregnant females}}{\text{Number of females mated}} \times 100$
Gestation index	$\frac{\text{Number of females bearing live pups}}{\text{Number of pregnant females}} \times 100$
Duration of gestation	Number of days between confirmation of mating and the beginning of parturition
Percentage live males at First Litter Check	$\frac{\text{Number of live male pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$
Percentage live females at First Litter Check	$\frac{\text{Number of live female pups at First Litter Check}}{\text{Number of live pups at First Litter Check}} \times 100$
Percentage of postnatal loss Days 0-4 *post partum*	$\frac{\text{Number of dead pups on Day 4 } \textit{post partum}}{\text{Number of live pups at First Litter Check}} \times 100$
Viability index	$\frac{\text{Number of live pups on Day 4 } \textit{post partum}}{\text{Number of pups born alive}} \times 100$

6.11. Electronic data capture

Observations/measurements in the study were recorded electronically using the following programme(s):
- REES version 1.5 (REES Scientific, Trenton, NJ, USA): Environmental monitoring.
- TOXDATA version 8.0 (NOTOX B.V., 's-Hertogenbosch, The Netherlands): Mortality / Clinical signs / Body weights / Food consumption / Reproduction processes / Observations offspring / Organ weights.
- Advia 120 Version V.3.1.8.0.MS (Bayer Diagnostics, Mijdrecht, The Netherlands): Haematology.
- Sta Compact version 1.06.06 (Stago Instruments, Gennevilliers, France): Clotting parameters
- Olympus AU 400 version 6 (Goffin-Meyvis, Etten-Leur, The Netherlands): Clinical laboratory investigations.
- MAMS version 6.2 (Pearson Technical Services, Suffolk, Great Britain): Motor activity measurement.

System control, data acquisition and data processing for analytical chemistry was performed using the following programme:
- Empower version 5.00 (Waters, Milford, MA, USA).

6.12. Interpretation

The following statistical methods were used to analyse the data:

- If the variables could be assumed to follow a normal distribution, the Dunnett-test (many-to-one t-test) based on a pooled variance estimate were applied for the comparison of the treated groups and the control groups for each sex (Ref. 1).

- The Steel-test (many-to-one rank test) was applied instead of the Dunnett-test if the data could not assumed to follow a normal distribution (Ref. 2).

- The Fisher-exact test was applied to frequency data (Ref. 3).

All tests were two-sided and in all cases $p < 0.05$ was accepted as the lowest level of significance.

Group means were calculated for continuous data and medians were calculated for discrete data (scores) in the summary tables. Test statistics were calculated on the basis of exact values for means and pooled variances. Individual values, means and standard deviations may have been rounded off before printing. Therefore, two groups may display the same printed means for a given parameter, yet display different test statistics values.

6.13. List of deviations

6.13.1. List of protocol deviations

1 Females 50 (Group 1), 51 and 55 (Group 2) and 73 (Group 4) which had shown no evidence of mating were anaesthetized using iso-flurane and subsequently exsanguinated on post-cohabitation Day 14, instead of post-cohabitation Day 24-26. These animals were erroneously removed from the study together with females with evidence of mating, which had not delivered on post-mating Day 24-26.
Females 50, 51 and 73 were not mated, but Female 55 showed normally developing implantations, e.g. 6 implantations left and 7 right, with sizes between 2.3 and 2.6 cm.
Evaluation: As a result, only information on breeding data and pup development from animal 55 is missing. As sufficient data is available to evaluate the effects in Group 2, the study integrity was not affected.

2 On 19 February no body weights were measured in the mating phase. These weights were determined on 20 February.
Evaluation: Body weight was determined weekly, a deviation of 1 day does not affect the study integrity.

3 On 17 February no food consumption was measured in the lactation phase. These weights were determined on 18 February
Evaluation: Food consumption was determined one day later. This provides sufficient information for evaluation of the results.

4 Mating of animals 43, 45, 59 and 79 was not detected (no sperm in vaginal lavage and no copulation plug noted). Therefore, from mating until lactation no food consumption was determined for these animals and body weights were determined weekly, instead of on Days 0, 4, 7, 11, 14, 17 and 20 *post-coitum.*
Evaluation: From all groups sufficient information is available to evaluate the effects on food consumption and body weights during post-coitum.

5 No vaginal wash was performed for animal 43 during mating phase on one day during the study period (27 January 2007).
Evaluation: Looking back at the data, the animal had mated on 24 January 2007. The vaginal wash on 27 January would not have resulted in relevant information.

6 A few tissues were not available for histopathology. Reasons for this included that these tissues were not discernable at necropsy or trimming, or were erroneously not collected at necropsy. Tissues are listed in raw data and pathology report.
Evaluation: Sufficient data was available for evaluation.

The study integrity was not adversely affected by the deviations.

6.13.2. List of standard operating procedure deviations

Any deviations from standard operating procedures were evaluated and filed in the study file. There were no deviations from standard operating procedures that affected the integrity of the study.

7. RESULTS

7.1. Analysis of Dose Preparations (see also Appendix 3)

The concentrations analysed in the formulations of Groups 2, 3 and 4 were in agreement with target concentrations (i.e. between 93% and 105%).

Small test substance peaks were observed in one of the samples of the Group 1 formulation. The maximum contribution to the other samples was 0.15% based on area. This was due to carry-over in the analytical system. In the second sample of the Group 1 formulation no test substance peaks were observed. Therefore, it was concluded that Group 1 did not contain any test substance.

The formulations of Group 2 and Group 4 were homogeneous (2.5% and 3.3% relative standard deviation, respectively).

Analysis of Group 2 and Group 4 formulations after 5 hours of storage at room temperature yielded a relative difference of –2.5% and –1.5%, respectively. Therefore, the samples were considered stable at room temperature for at least at 5 hours.

7.2. Observations

7.2.1. Mortality

No treatment related mortality occurred during the study period.

Two females were sacrificed before the end of the study period. One animal treated at 50 mg/kg (Female 60) was sacrificed as the animal was cannibalizing the pups on Day 1 of lactation and one female at 500 mg/kg (Female 79) was sacrificed due to total litter loss on Day 2 of lactation. This animal had five pups, three pups were found dead on Day 1 of lactation, and two other pups were found dead on Day 2 of lactation.

7.2.2. Clinical Signs

Slight to moderate salivation was noted in all males and females treated at 500 mg/kg. Furthermore, incidentally rales were noted in two males at 500 mg/kg (Males 37 and 38) and piloerection was noted in one female at 500 mg/kg (Female 79) at the end of treatment.

Yellow discolouration of the urine was noted in all animals of Groups 2, 3 and 4 in a dose dependant manner.

Other clinical signs (slight salivation, scabs, chromodacryorrhoea, broken tail apex, diarrhoea and alopecia) were considered to be unrelated to treatment.

7.2.3. Body Weights:

Slightly reduced body weight and body weight gain was noted in males treated at 500 mg/kg during the complete study period (not always statistically significant). Reduced body weight and body weight gain was also noted in females treated at 500 mg/kg on Days 14 to 20 *post-coitum* and during lactation (not always statistically significant).

7.2.4. Food Consumption

Food consumption before or after allowance for body weight was reduced during lactation in females treated at 500 mg/kg (statistically not significant).

Other changes in food consumption were considered to be of no toxicological relevance.

7.2.5. Functional observations

Hearing ability, pupillary reflex, static righting reflex and grip strength were normal in all animals.

The motor activity test showed an increase in activity at the low sensor for females at 500 mg/kg. No other effects were noted in the motor activity test.

7.3. Clinical Laboratory Investigations

7.3.1. Haematology

A decrease in relative number of eosinophils was noted in males and females at 500 mg/kg.

Furthermore, a slight increase in red blood cell distribution width was noted in males at 500 mg/kg. However as no corroborative findings were noted in related parameters this finding was considered to be of no toxicological relevance.

Other findings achieving statistical significance (increased APTT in males at 50 and 150 mg/kg) were considered to be of no toxicological relevance in absence of a dose response relationship.

7.3.2. Clinical Biochemistry

Treatment related effects were mainly noted in males treated at 500 mg/kg. These findings comprised high alanine aminotransferase, aspartate aminotransferase (also noted in females at 500 mg/kg) and alkaline phosphatase activities and high cholesterol levels. Cholesterol levels were also increased in males treated at 150 mg/kg, but to a lesser extent.

Furthermore, calcium levels were increased in males and females at 500 mg/kg.

Other findings achieving statistical significance (decreased potassium levels in males at 50 mg/kg and increased albumin in females at 150 mg/kg) were considered to be of no toxicological relevance in absence of a dose response relationship.

7.4. Pathology

7.4.1. Macroscopic Examination

Pale discolouration of the liver was noted in five males treated at 500 mg/kg. Furthermore, many grey-white foci were found on the lungs of 4 females treated at 500 mg/kg.

One female at 50 mg/kg (Female 60) showed reddish contents in the stomach. This animal was sacrificed due to cannibalism of the pups.

One female at 50 mg/kg (Female 51) showed an enlarged cervix and uterus. The uterus was filled with fluid. These were signs of pseudo pregnancy and were considered to be unrelated to treatment.

Incidental findings among control and treated animals included an enlarged adrenal gland, pelvic dilation of the kidney, reduced size of the seminal vesicles, bent tail apex (correlating to the broken tail apex noted at clinical observations), alopecia, dark red discolouration of the mandibular lymph nodes and diaphragmatic hernia of the liver. These findings are occasionally seen among rats used in these types of study and/or in the absence of a dose response relationship they were considered changes of no toxicological significance.

7.4.2. Organ Weights

Liver/body weight ratios were increased with statistical significance for males treated at 500 mg/kg, which correlated with the findings at macroscopic and microscopic examination.

Decreased thymus weight and thymus/body weight ratios was noted in males and females treated at 500 mg/kg and correlated in some animals with the atrophy noted at microscopic examination. Furthermore, increased kidney weight was noted in females at 500 mg/kg, which correlated in some animals with the observed basophilia. However, as these microscopic findings were not considered to be related to treatment, the toxicological relevance of these organ weight changes remains unclear.

Other changes in organ weight comprised increased heart weight in males at 50, 150 and 500 mg/kg and females at 500 mg/kg, decreased epididymides weight in males at 500 mg/kg, increased relative brain weight in males at 500 mg/kg and increased adrenal weight in females at 150 and 500 mg/kg.

Other changes (increased liver weight in females at 50 mg/kg, decreased testes weight in males at 50 mg/kg) were considered to be of no toxicological relevance in absence of a dose response relationship.

7.4.3. Microscopic Examination (see also Appendix 4)

In the ***lungs***, *alveolar macrophage foci* were noted at a minimal degree in one group 3 (150 mg/kg/day) and at a slight degree in one group 4 male animals. In females this finding was present at a slight degree of severity in one Group 1 (0 mg/kg/day, control) and at slight or moderate severity in five group 4 animals which was significantly increased ($p < 0.05$). In the same organ *lymphocytic alveolar inflammation* was recorded at a slight degree in one group 1, minimal in one group 3 and also at a minimal degree in four group 4 males. In females, one animal in each of Groups 1, 2 (50 mg/kg/day) and 3 recorded this finding at a minimal degree and in Group 4, five animals at minimal to moderate degree. Again this was significantly increased in Group 4 females ($p < 0.05$) and there was a positive trend ($p < 0.05$) in males. These findings correlated to the gray-white foci observed in females at 500 mg/kg. At macroscopy, these findings were not observed in males.

In the ***liver***, *hepatocellular vacuolation* at a minimal or slight degree was seen in four Group 4 males and in three group 4 females. This incidence did not reach statistical significance in either sex, however there was a positive trend (p at least <0.05) for both sexes. This finding was the microscopic correlate to the pale discolouration in this organ noted at necropsy.

Corticomedullary tubular basophilia at a minimal or slight degree was recorded in the ***kidneys*** of males: two in Group 1, one in Group 3 and two in Group 4; in females: one in Group 1 and three in Groups 2 and 4. This was neither significantly increased or positive in trend for either sex.

In the ***adrenal glands*** of males *vacuolation in the zona fasiculata* was seen at a minimal degree in two group one, two group 2, slight degree in one group 3 and at minimal or slight degree in four group 4 animals. This slight increase in group 4 was not significant, however again there was a positive trend ($p < 0.05$).

Lymphoid atrophy – involution of the ***thymus*** was recorded in males: at minimal degree one group 1, slight in one group 3 and slight in two group 4 animals; in females: at minimal to moderate in four group 1, minimal in one group 3 and slight or moderate in three group 4 animals. This was neither significantly increased or positive in trend for either sex.

In males suspected of infertility, there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. The spermatogenic staging profiles were normal for all group 1 and group 4 males evaluated.

In females suspected of infertility, animal 75 (group 4) had *endometrial inflammation.* Animals *73* and 77 (group 4) had vaginal *epithelial mucification* (possible oestrus cycle disturbance). In animals 50 (control), 60 (Group 2) and 79 (Group 4), there were no findings to account for infertility. Animal 51 (group 2) exhibited *endometrial squamous metaplasia and* animal 55 (group 2) had a *deciduoma.* As no similar findings were noted at the mid or high dose group, the toxicological relevance of these findings was doubted.

The remainder of the recorded microscopic findings were within the range of background pathology encountered in Wistar rats of this age and occurred at similar incidences and severity in both control and treated rats.

7.5. Reproduction

A decrease in gestation index was noted in females at 500 mg/kg.

No effect was noted on the duration of gestation and precoital time at 50, 150 or 500 mg/kg.

Erroneously, one female treated at 50 mg/kg (Female 55) was sacrificed before the end of gestation. This female was found to be pregnant and showed 13 normally developing implantations (six in the left uterus horn and seven in the right uterus horn), with crown-rump lengths ranging from 2.3 to 2.6 cm. No mating date was available for this animal, e.g. no mating was detected by lavage or vaginal plug, therefore no record is available on which day of gestation this animal was sacrificed.

Reproduction parameters are described in tables I and II below:

Table I. Reproduction Data.

Number of females	Group 1 Control	Group 2 50 mg/kg	Group 3 150 mg/kg	Group 4 500 mg/kg
Paired	10	10	10	10
Mated	9	9	10	9
Non-pregnant	-	-	-	-
Implantations sites only	-	-	-	2
Pregnant	9	9	10	9
Number of females with living pups at first litter check	9	8*	10	7

* Female 55 was pregnant with normally developing implantations, but was erroneously sacrificed before the end of gestation (see protocol deviations).

Table II. Fertility F_0-generation.

	Group 1 Control	Group 2 50 mg/kg	Group 3 150 mg/kg	Group 4 500 mg/kg
Percentage mating (Females mated / Females paired) * 100	90	90	100	90
Fertility index (Females achieving a pregnancy / Females paired) * 100	90	90	100	90
Conception rate (Females achieving a pregnancy / Females mated) * 100	100	100	100	100
Gestation index (Number of females with living pups at first litter check/ Number of females pregnant) * 100	100	88.9*	100	77.8

* Female 55 was pregnant with normally developing implantations, but was erroneously sacrificed before the end of gestation (see protocol deviations).

7.6. Breeding Data

At the first litter check, the average and total number of living pups per litter was reduced at 500 mg/kg (average of 6.9 pups per litter) when compared to concurrent controls (average of 16.0 pups per litter).

Furthermore, an increased incidence in postnatal loss was noted at 50, 150 and 500 mg/kg, resulting in a reduced viability index. No dose response relationship could be established between the treated groups.

7.7. Pup Development

There was an increased incidence in missing and cannibalized pups, correlating with the increased post natal loss noted at 50, 150 and 500 mg/kg when compared to the concurrent controls. The increased incidence in postnatal loss might be caused by possible developmental effects.

(Mean) body weights were similar for the control and treated groups.

Incidental findings consisted of a small, pale or weak appearance, red spot or discolouration (neck, head, back, tail and/or tail apex), scab (hindleg, nose), wound (nose), blue discolouration abdomen and swelling of the head. Macroscopic examination of the pups revealed no milk in the stomach and a small appearance. No relationship with treatment was established for these observations or they were considered to be within the normal biological variation for rats of this age and strain.

8. DISCUSSION AND CONCLUSION

Dytek® DCH-99 was administered by daily oral gavage to male and female Wistar rats at dose levels of 0, 50, 150 and 500 mg/kg/day. The males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 31 days). The females were exposed for 2 weeks prior to mating, during mating, during *post-coitum*, and at least 3 days of lactation (for 42 to 45 days).

Formulation analysis showed that the formulations were prepared accurately, were homogeneous and were stable for at least 5 hours at room temperature.

Parental toxicity
No treatment related mortality occurred during the study period.

Slight to moderate salivation was noted in all males and females treated at 500 mg/kg. Furthermore, incidentally rales were noted in two males at 500 mg/kg and piloerection was noted in one female at 500 mg/kg at the end of treatment.

Yellow discolouration of the urine was noted in all animals of Groups 2, 3 and 4 in a dose dependant manner. This could be due to excretion of the test compound or a metabolite in the urine. Without corroborative findings for clinical biochemistry parameters and as no macroscopic or microscopic abnormalities of the kidneys were observed, this finding was not considered toxicological relevant.

At 500 mg/kg, reduced body weight gain was noted in males during the treatment period and in females on Days 14 to 20 *post-coitum* and during lactation (not always statistically significant). Furthermore, at 500 mg/kg food consumption before or after allowance for body weight was reduced during lactation in females (statistically not significant).

Hearing ability, pupillary reflex, static righting reflex and grip strength were normal in all animals. The motor activity test showed an increase in activity at the low sensor for females at 500 mg/kg, which might be due to hyperactivity of the dam and/or pups.

At 500 mg/kg, a treatment related decrease in eosinophils was noted in males and females.

At 500 mg/kg, a treatment related decrease in eosinophils was noted in males and females. Furthermore, treatment related effects were noted in clinical biochemistry (mainly in males). These findings comprised high alanine aminotransferase, aspartate aminotransferase activities (also noted in females at 500 mg/kg) and alkaline phosphatase activities and high cholesterol levels. Cholesterol levels were also increased in males treated at 150 mg/kg, but to a lesser extent. These findings at 500 mg/kg correlated with the macroscopic or microscopic effects on the liver, e.g. pale discolouration, increased liver/body weight ratios and hepatocellular vacuolation of the liver at a minimal or slight degree. In addition, calcium levels were increased in males and females at 500 mg/kg.

Besides microscopic changes in the liver, minor treatment related morphological alterations were noted in the lungs and adrenal glands:

In the lungs, alveolar macrophage foci were increased in incidence and severity to moderate in females at 500 mg/kg. In the same organ lymphocytic alveolar inflammation was slightly increased in incidence in males and in incidence and severity to moderate in females. These findings correlated with the grey-white foci observed in females at 500 mg/kg.

In the adrenal glands of males vacuolation in the zona fasiculata at minor degrees of severity was slightly increased in incidence at 500 mg/kg which was not statistically significant. However there was a positive trend.

The findings in liver, lung and adrenal glands were chiefly minor in nature and may be regarded as either slight increases in spontaneously occurring conditions or adaptive. As such they were

considered to be indicators of slight toxicity to the test-item.

The organ weight changes in thymus and kidney correlated with the microscopic findings in these organs, e.g. atrophy and basophilia respectively. No corroborative findings were noted for the changes in weight of the heart, epididymides and brain. These changes were mild in nature and in absence of corroborative findings or a clear dose response relationship, the toxicological relevance of these changes remains unclear.

Reproductive toxicity
The gestation index was decreased in females at 500 mg/kg. No effect was noted on the duration of gestation and precoital time at 50, 150 or 500 mg/kg.

Of all animals, three females did not mate (one in the control group, one in the low dose group and one in the high dose group) and two females had implantations sites only (high dose group).

In males suspected of infertility, there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. Further, the spermatogenic staging profiles were normal for all Group 1 and Group 4 males evaluated.

In females suspected of infertility, animal 75 (group 4) had endometrial inflammation. Animals 73 and 77 (group 4) had vaginal epithelial mucification (possible oestrus cycle disturbance).

Breeding toxicity
At 500 mg/kg, the average and total number of living pups per litter was reduced at the first litter check, (average of 6.9 pups per litter) when compared to concurrent controls (average of 16.0 pups per litter).

An increased incidence in postnatal loss (due to increased cannibalism) was noted at 50, 150 and 500 mg/kg, resulting in a reduced viability index. No dose response relationship could be established between the treated groups.

Developmental toxicity
There was an increased incidence in missing and cannibalized pups, correlating with the increased post natal loss noted at 50, 150 and 500 mg/kg when compared to the concurrent controls.

In surviving pups no treatment related changes in developmental indices were noted. Furthermore, (mean) body weights were similar for the control and treated groups.

CONCLUSION

In conclusion, treatment with Dytek® DCH-99 by oral gavage in male and female Wistar rats at dose levels of 0, 50, 150 and 500 mg/kg/day revealed parental and reproduction toxicity at 500 mg/kg body weight/day. Breeding and developmental toxicity, e.g. increased incidence of postnatal loss, cannibalism and/or missing pups was observed at all treated groups. Although no dose response relationship could be established, the observed increase was considered to be related to treatment as no such increased incidence was noted in concurrent and historical control data.

Based on these findings, the parental and reproduction No Observed Adverse Effect Level (NOAEL) was established at 150 mg/kg body weight/day. No breeding NOAEL could be established.

Based on results in surviving pups, the developmental NOAEL was established at 500 mg/kg. However, the cause of the observed cannibalism was unclear and might be related to developmental effects, which will then affect the NOAEL.

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APPENDIX 1 FIGURES AND SUMMARY TABLES

CLINICAL SIGNS SUMMARY
MALES

		PRE MATING	REPRO PHASE
SIGN (MAX. GRADE)	WEEK:	1	1 4
(LOCATION)	DAY:	123456712345671234567123456712345671234567123	

GROUP 1 (CONTROL)

Skin / fur / plumage		
Scabs (3)	G:	.....1111111.....
(Ear right)	%:	.....1111111.....
Secretion / excretion		
Chromodacryorrhoea (3)	G:	1
(Eye right)	%:	1
Various		
Broken (1)	G:	11111111111111111111111111111111
(Tail apex)	%:	11111111111111111111111111111111

GROUP 2 (50 MG/KG)

Skin / fur / plumage		
Yellow discolouration (1)	G:	1111111111111111
(Urine)	%:	.....AAAAAAAAAAAAAAAA
Various		
Broken (1)	G:	.1111111111111111111111111111111
(Tail apex)	%:	.1111111111111111111111111111111

GROUP 3 (150 MG/KG)

Skin / fur / plumage		
Yellow discolouration (1)	G:	...1111111111111111111111111111
(Urine)	%:	...AAAAAAAAAAAAAAAAAAAAAAAAAA
Secretion / excretion		
Diarrhoea (1)	G:	.....1.....
	%:	.....1.....

GROUP 4 (500 MG/KG)

Breathing		
Rales (3)	G:	.....11.....
	%:	.....11.....
Skin / fur / plumage		
Yellow discolouration (1)	G:	.1111111111111111111111111111
(Urine)	%:	.AAAAAAAAAAAAAAAAAAAAAAAAAA
Secretion / excretion		
Salivation (3)	G:	.....1.1111111111111111111
	%:	.....1.3444AAAAAAAAAAAAAAAA

FEMALES

		PRE MATING	REPRO PHASE
SIGN (MAX. GRADE)	WEEK:	1	1 4
(LOCATION)	DAY:	123456712345671234567123456712345671234567123	

GROUP 1 (CONTROL)

Skin / fur / plumage		
Alopecia (3)	G:	.....1..
(Chest)	%:	.....1..
Alopecia (3)	G:	.....1..
(Foreleg right)	%:	.....1..
Alopecia (3)	G:	.....1111222222....
(Hindleg right)	%:	.....1111111111....
Alopecia (3)	G:	.....122233333333..
(Forelegs)	%:	.....1111111111..
Alopecia (3)	G:	.....22..
(Hindlegs)	%:	.....11..

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)
.: Observation performed, sign not present

CLINICAL SIGNS SUMMARY
FEMALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE
	WEEK:	1.............1....................4.........
	DAY:	123456712345671234567123456712345671234567123
GROUP 2 (50 MG/KG)		
Skin / fur / plumage		
Alopecia (3)	G:	...........1111111...........................
(Neck)	%:	...........1111111...........................
Alopecia (3)	G:	1111111111111111111111111111111111111111111..
(Thigh hind right)	%:	1111111111111111111111111111111111111111111..
Scabs (3)	G:	.........11..................................
(Neck)	%:	.........11..................................
Yellow discolouration (1)	G:	1111111111111111111111111111111
(Urine)	%:	..............AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
Secretion / excretion		
Salivation (3)	G:	.....................................1111....
	%:	.....................................1111....
GROUP 3 (150 MG/KG)		
Skin / fur / plumage		
Yellow discolouration (1)	G:	...111111111111111111111111111111111111111111
(Urine)	%:	...AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
GROUP 4 (500 MG/KG)		
Skin / fur / plumage		
Piloerection (1)	G:	..................................11.11111...
	%:	..................................11.11111...
Yellow discolouration (1)	G:	..1111111111111111111111111111111111111111111
(Urine)	%:	..AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA**A5
Secretion / excretion		
Salivation (3)	G:	...111111111111111111111111111111111111111111
	%:	...335399AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA**A5

G: Median value of the highest individual daily grades
%: Percent of affected animals (0=less than 5%, 1=between 5% and 15%,..., A=more than 95%)
.: Observation performed, sign not present

BODY WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAY 1	MEAN	335	335	338	339
WEEK 1	ST.DEV	11.7	9.5	9.0	11.0
	N	10	10	10	10
DAY 8	MEAN	372	366	372	360
WEEK 2	ST.DEV	14.7	12.2	11.5	14.4
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	404	401	401	397
WEEK 1	ST.DEV	17.2	16.9	21.3	16.4
	N	10	10	10	10
DAY 8	MEAN	427	419	419	402 *
WEEK 2	ST.DEV	20.1	20.5	27.8	18.6
	N	10	10	10	10
DAY 15	MEAN	448	438	442	430
WEEK 3	ST.DEV	26.0	22.1	32.3	17.6
	N	10	10	10	10

FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAY 1	MEAN	228	230	229	229
WEEK 1	ST.DEV	7.7	7.8	11.2	10.1
	N	10	10	10	10
DAY 8	MEAN	239	239	236	237
WEEK 2	ST.DEV	9.1	5.7	12.4	8.9
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	247	246	246	246
WEEK 1	ST.DEV	8.4	13.9	15.5	10.0
	N	10	10	10	10
DAY 8	MEAN	276	278		265
WEEK 2	ST.DEV	13.7	12.1		0.0
	N	3	3		2
DAY 15	MEAN	293	294		282
WEEK 3	ST.DEV	19.0	28.2		19.8
	N	3	3		2
DAY 22	MEAN	346	348		316
WEEK 4	ST.DEV	55.4	61.8		29.0
	N	3	3		2
DAY 29	MEAN	292	332		296
WEEK 5	ST.DEV	---	41.0		---
	N	1	2		1

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHTS (GRAM) SUMMARY
FEMALES
F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
POST COITUM					
DAY 0	MEAN	250	251	248	251
	ST.DEV.	13.3	10.4	14.8	9.4
	N	7	7	10	6
DAY 4	MEAN	271	274	265	265
	ST.DEV.	9.5	15.7	15.5	15.9
	N	7	7	10	6
DAY 7	MEAN	282	283	273	278
	ST.DEV.	10.8	17.1	14.2	19.3
	N	7	7	10	6
DAY 11	MEAN	302	305	293	301
	ST.DEV.	14.0	18.2	21.9	21.7
	N	7	7	10	6
DAY 14	MEAN	321	325	312	308
	ST.DEV.	12.7	20.4	21.5	23.4
	N	7	7	10	6
DAY 17	MEAN	363	367	352	334 *
	ST.DEV.	16.1	25.2	22.3	19.6
	N	7	7	10	6
DAY 20	MEAN	418	418	409	368 **
	ST.DEV.	20.0	36.9	27.0	20.8
	N	7	7	10	6
LACTATION					
DAY 1	MEAN	306	324	301	296
	ST.DEV.	15.6	26.2	24.4	18.2
	N	9	8	10	7
DAY 4	MEAN	320	328	314	302
	ST.DEV.	11.7	19.1	22.1	16.6
	N	9	7	10	7

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

BODY WEIGHT GAIN (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	10	10	10
DAY 8	MEAN	11	9	10	6 **
WEEK 2	ST.DEV	2.0	2.2	3.7	1.8
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	21	19	19	17
WEEK 1	ST.DEV	4.0	3.4	6.1	3.6
	N	10	10	10	10
DAY 8	MEAN	28	25	24	19 **
WEEK 2	ST.DEV	5.5	5.1	8.0	4.7
	N	10	10	10	10
DAY 15	MEAN	34	31	31	27
WEEK 3	ST.DEV	6.8	5.3	9.5	4.8
	N	10	10	10	10

FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAY 1	MEAN	0	0	0	0
WEEK 1	ST.DEV	0.0	0.0	0.0	0.0
	N	10	10	10	10
DAY 8	MEAN	5	4	3	3
WEEK 2	ST.DEV	2.0	3.0	2.4	3.2
	N	10	10	10	10
MATING PERIOD					
DAY 1	MEAN	8	7	8	8
WEEK 1	ST.DEV	4.0	4.6	2.7	5.0
	N	10	10	10	10
DAY 8	MEAN	21	21		16
WEEK 2	ST.DEV	3.9	2.0		7.2
	N	3	3		2
DAY 15	MEAN	29	28		24
WEEK 3	ST.DEV	7.7	12.3		16.4
	N	3	3		2
DAY 22	MEAN	52	52		39
WEEK 4	ST.DEV	24.4	27.0		21.3
	N	3	3		2
DAY 29	MEAN	28	44		24
WEEK 5	ST.DEV	---	12.1		---
	N	1	2		1

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

BODY WEIGHT GAIN (%) SUMMARY
FEMALES
F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
POST COITUM					
DAY 0	MEAN	0	0	0	0
	ST.DEV.	0.0	0.0	0.0	0.0
	N	7	7	10	6
DAY 4	MEAN	9	9	7	6
	ST.DEV.	2.7	3.3	2.5	3.1
	N	7	7	10	6
DAY 7	MEAN	13	13	10	11
	ST.DEV.	3.0	3.8	3.6	4.7
	N	7	7	10	6
DAY 11	MEAN	21	22	18	20
	ST.DEV.	3.1	4.8	6.1	5.2
	N	7	7	10	6
DAY 14	MEAN	28	30	26	23
	ST.DEV.	3.2	5.1	5.1	5.5
	N	7	7	10	6
DAY 17	MEAN	45	46	42	33 **
	ST.DEV.	3.3	6.9	4.8	4.1
	N	7	7	10	6
DAY 20	MEAN	67	67	65	47 **
	ST.DEV.	4.8	11.0	7.3	4.2
	N	7	7	10	6
LACTATION					
DAY 1	MEAN	0	0	0	0
	ST.DEV.	0.0	0.0	0.0	0.0
	N	9	8	10	7
DAY 4	MEAN	5	3	4	2
	ST.DEV.	3.7	5.2	4.5	3.5
	N	9	7	10	7

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAYS 1-8	MEAN	29	28	28	28
WEEKS 1-2	ST.DEV	0.4	0.3	0.4	0.3
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	30	29	30	32 **
WEEKS 2-3	ST.DEV	0.3	0.2	0.1	0.6
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATING	MEAN	29	29	29	30

FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAYS 1-8	MEAN	19	19	19	19
WEEKS 1-2	ST.DEV	0.5	0.6	1.2	1.9
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	20	20	20	22
WEEKS 2-3	ST.DEV	0.1	0.6	0.8	1.3
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATING	MEAN	20	20	20	21

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

FOOD CONSUMPTION (G/ANIMAL/DAY) SUMMARY
FEMALES
F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
POST COITUM					
DAYS 0-4	MEAN	24	24	22	23
	ST.DEV.	2.4	3.6	1.6	3.2
	N	7	7	10	6
DAYS 4-7	MEAN	23	23	23	25
	ST.DEV.	1.3	3.3	6.5	4.2
	N	7	7	10	6
DAYS 7-11	MEAN	25	26	24	25
	ST.DEV.	2.9	2.1	2.4	3.8
	N	7	7	10	6
DAYS 11-14	MEAN	28	32	26	30
	ST.DEV.	3.4	6.5	3.1	3.6
	N	7	7	10	6
DAYS 14-17	MEAN	33	32	29 *	31
	ST.DEV.	3.3	1.2	2.4	2.6
	N	7	7	10	6
DAYS 17-20	MEAN	32	34	30	31
	ST.DEV.	2.8	3.5	2.4	3.7
	N	7	7	10	6
MEAN OF MEANS		28	29	26	28
LACTATION					
DAYS 1-4	MEAN	35	40	42	23
	ST.DEV.	5.6	12.3	18.5	5.6
	N	9	7	10	7

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAYS 1-8	MEAN	78	76	76	79
WEEKS 1-2	ST.DEV	0.3	0.0	0.8	2.3
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	81	80	80	89 **
WEEKS 2-3	ST.DEV	1.7	1.6	0.0	0.2
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATING	MEAN	79	78	78	84

FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
PRE MATING					
DAYS 1-8	MEAN	81	81	81	80
WEEKS 1-2	ST.DEV	0.9	3.7	2.9	5.1
	N (CAGE)	2	2	2	2
DAYS 8-15	MEAN	83	84	85	93 *
WEEKS 2-3	ST.DEV	1.7	3.7	1.3	2.1
	N (CAGE)	2	2	2	2
MEAN OF MEANS					
OVER PRE MATING	MEAN	82	82	83	87

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) SUMMARY
FEMALES
F0-GENERATION

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
POST COITUM					
DAYS 0-4	MEAN	88	87	83	87
	ST.DEV.	7.4	8.5	5.3	8.9
	N	7	7	10	6
DAYS 4-7	MEAN	83	83	86	89
	ST.DEV.	4.2	7.2	26.5	9.6
	N	7	7	10	6
DAYS 7-11	MEAN	83	86	82	84
	ST.DEV.	7.9	7.3	4.7	8.0
	N	7	7	10	6
DAYS 11-14	MEAN	88	101	84	96
	ST.DEV.	9.4	23.3	5.1	7.2
	N	7	7	10	6
DAYS 14-17	MEAN	90	88	82	92
	ST.DEV.	9.4	4.8	6.5	6.6
	N	7	7	10	6
DAYS 17-20	MEAN	77	82	74	85
	ST.DEV.	4.6	7.1	5.1	6.9
	N	7	7	10	6
MEAN OF MEANS		85	88	82	89
LACTATION					
DAYS 1-4	MEAN	108	121	135	75
	ST.DEV.	15.2	31.4	56.0	17.5
	N	9	7	10	7

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level
Explanations for excluded data are listed in the tables of the individual values

FUNCTIONAL OBSERVATIONS SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
TREATMENT					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5
GRIP	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	5

FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
TREATMENT					
HEARING	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	6
PUPIL L	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	6
PUPIL R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	6
STATIC R	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	6
GRIP	MEDIAN	0	0	0	0
SCORE 0/1	N	5	5	5	6

+/++ Steel-test significant at 5% (+) or 1% (++) level

MOTOR ACTIVITY MEASUREMENTS SUMMARY

MALES
WEEK 4

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
total high sensor count	MEAN	2048	1915	2868	2262
	ST.DEV	642	1306	487	370
	N	5	5	5	5
total low sensor count	MEAN	4589	4415	4802	5448
	ST.DEV	1342	714	685	1381
	N	5	5	5	5

FEMALES
LACTATION

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
total high sensor count	MEAN	3244	1078	1179	2288
	ST.DEV	5360	358	355	2404
	N	5	5	5	5
total low sensor count	MEAN	3961	4068	3549	7093 **
	ST.DEV	496	1483	833	1599
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

HAEMATOLOGY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
WBC	MEAN	9.8	10.2	9.0	10.6
10E9/l	ST.DEV	1.7	1.9	1.0	1.1
	N	5	5	5	5
Neutrophils	MEAN	17.3	13.1	13.0	17.4
%WBC	ST.DEV	6.1	2.4	1.0	6.3
	N	5	5	5	5
Lymphocytes	MEAN	76.8	83.3	82.4	78.4
%WBC	ST.DEV	7.2	2.5	2.0	6.4
	N	5	5	5	5
Monocytes	MEAN	3.9	2.1	2.9	3.5
%WBC	ST.DEV	1.4	0.6	1.2	2.1
	N	5	5	5	5
Eosinophils	MEAN	1.6	1.2	1.3	0.4 +
%WBC	ST.DEV	0.5	0.1	0.5	0.3
	N	5	5	5	5
Basophils	MEAN	0.4	0.5	0.4	0.3
%WBC	ST.DEV	0.3	0.1	0.1	0.2
	N	5	5	5	5
Red blood cells	MEAN	8.40	8.30	8.52	8.12
10E12/l	ST.DEV	0.15	0.24	0.39	0.28
	N	5	5	5	5
Reticulocytes	MEAN	2.9	3.1	3.1	3.4
%RBC	ST.DEV	0.6	0.4	0.4	0.4
	N	5	5	5	5
RDW	MEAN	11.8	12.6	12.7	13.0 *
%	ST.DEV	0.4	0.6	0.7	0.7
	N	5	5	5	5
Haemoglobin	MEAN	9.7	9.5	9.6	9.5
mmol/l	ST.DEV	0.3	0.5	0.1	0.3
	N	5	5	5	5
Haematocrit	MEAN	0.439	0.424	0.431	0.422
l/l	ST.DEV	0.019	0.022	0.009	0.012
	N	5	5	5	5
MCV	MEAN	52.2	51.1	50.6	52.0
fl	ST.DEV	2.5	2.3	2.2	1.7
	N	5	5	5	5
MCH	MEAN	1.15	1.15	1.13	1.17
fmol	ST.DEV	0.04	0.06	0.05	0.05
	N	5	5	5	5
MCHC	MEAN	22.14	22.44	22.26	22.47
mmol/l	ST.DEV	0.28	0.28	0.31	0.30
	N	5	5	5	5
Platelets	MEAN	901	1056	1025	981
10E9/l	ST.DEV	215	120	88	245
	N	5	5	5	5
PT	MEAN	18.2	17.5	18.0	18.0
s	ST.DEV	0.8	0.6	0.6	0.8
	N	5	5	5	5
APTT	MEAN	11.7	17.3 **	15.7 *	15.0
s	ST.DEV	1.6	1.2	3.0	2.6
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

HAEMATOLOGY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
WBC	MEAN	7.3	5.0	5.0	5.8
10E9/l	ST.DEV	2.5	1.5	1.5	1.4
	N	5	5	5	5
Neutrophils	MEAN	19.2	21.5	23.1	27.5
%WBC	ST.DEV	4.1	5.5	5.1	12.1
	N	5	5	5	5
Lymphocytes	MEAN	77.4	74.6	73.3	68.9
%WBC	ST.DEV	4.0	6.3	5.7	12.4
	N	5	5	5	5
Monocytes	MEAN	2.2	2.7	2.6	3.0
%WBC	ST.DEV	0.5	1.4	0.7	0.6
	N	5	5	5	5
Eosinophils	MEAN	1.0	1.1	0.7	0.3 +
%WBC	ST.DEV	0.4	1.2	0.3	0.2
	N	5	5	5	5
Basophils	MEAN	0.3	0.1	0.2	0.3
%WBC	ST.DEV	0.1	0.2	0.1	0.1
	N	5	5	5	5
Red blood cells	MEAN	7.62	7.49	7.49	7.39
10E12/l	ST.DEV	0.27	0.39	0.42	0.73
	N	5	5	5	5
Reticulocytes	MEAN	6.0	5.6	6.9	6.0
%RBC	ST.DEV	2.3	1.0	2.5	2.3
	N	5	5	5	5
RDW	MEAN	15.0	16.1	15.5	15.3
%	ST.DEV	1.7	1.6	1.7	1.9
	N	5	5	5	5
Haemoglobin	MEAN	9.1	8.9	9.0	8.8
mmol/l	ST.DEV	0.6	0.4	0.5	0.6
	N	5	5	5	5
Haematocrit	MEAN	0.409	0.401	0.409	0.397
l/l	ST.DEV	0.018	0.017	0.021	0.022
	N	5	5	5	5
MCV	MEAN	53.7	53.6	54.7	54.0
fl	ST.DEV	0.9	3.0	2.0	2.6
	N	5	5	5	5
MCH	MEAN	1.20	1.20	1.20	1.20
fmol	ST.DEV	0.04	0.06	0.03	0.05
	N	5	5	5	5
MCHC	MEAN	22.34	22.33	21.88	22.25
mmol/l	ST.DEV	0.49	0.42	0.35	0.50
	N	5	5	5	5
Platelets	MEAN	1342	1200	1439	1317
10E9/l	ST.DEV	196	315	385	233
	N	5	5	5	5
PT	MEAN	17.4	16.8	17.3	18.0
s	ST.DEV	0.3	0.9	0.8	1.4
	N	5	5	5	5
APTT	MEAN	18.0	16.8	16.6	17.5
s	ST.DEV	1.4	3.5	2.7	3.7
	N	5	5	5	5

+/++ Steel-test significant at 5% (+) or 1% (++) level
*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
ALAT	MEAN	37.5	38.4	45.9	65.5 **
U/l	ST.DEV	4.5	7.8	11.6	3.0
	N	5	5	5	5
ASAT	MEAN	73.9	71.7	78.8	96.5 **
U/l	ST.DEV	5.9	4.8	6.7	8.1
	N	5	5	5	5
ALP	MEAN	103	111	113	149 **
U/l	ST.DEV	25	7	11	22
	N	5	5	5	5
Total protein	MEAN	62.3	62.8	63.4	63.1
g/l	ST.DEV	2.2	3.0	2.9	3.0
	N	5	5	5	5
Albumin	MEAN	31.0	31.0	31.2	31.4
g/l	ST.DEV	0.9	0.7	1.2	1.4
	N	5	5	5	5
Total bilirubin	MEAN	2.4	2.6	2.6	2.8
umol/l	ST.DEV	0.2	0.4	0.3	0.3
	N	5	5	5	5
Urea	MEAN	6.2	5.8	6.0	6.9
mmol/l	ST.DEV	0.6	0.9	1.1	0.4
	N	5	5	5	5
Creatinine	MEAN	39.0	38.5	37.5	39.0
umol/l	ST.DEV	2.2	0.8	1.8	2.0
	N	5	5	5	5
Glucose	MEAN	8.06	8.72	8.35	9.00
mmol/l	ST.DEV	0.66	1.12	1.59	1.17
	N	5	5	5	5
Cholesterol	MEAN	1.52	1.88	2.04 **	2.49 **
mmol/l	ST.DEV	0.23	0.34	0.19	0.17
	N	5	5	5	5
Sodium	MEAN	142.4	142.6	141.5	141.7
mmol/l	ST.DEV	0.7	1.1	0.8	0.6
	N	5	5	5	5
Potassium	MEAN	4.26	3.77 **	4.05	4.03
mmol/l	ST.DEV	0.25	0.18	0.09	0.17
	N	5	5	5	5
Chloride	MEAN	103	103	103	103
mmol/l	ST.DEV	1	1	1	1
	N	5	5	5	5
Calcium	MEAN	2.75	2.70	2.81	2.92 **
mmol/l	ST.DEV	0.05	0.07	0.06	0.07
	N	5	5	5	5
Inorg.Phos	MEAN	2.54	2.20	2.33	2.69
mmol/l	ST.DEV	0.20	0.25	0.18	0.19
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

CLINICAL BIOCHEMISTRY SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
ALAT	MEAN	58.1	57.9	50.6	65.0
U/l	ST.DEV	5.7	12.7	4.1	12.8
	N	5	5	5	5
ASAT	MEAN	75.2	74.3	71.7	96.0 *
U/l	ST.DEV	7.3	12.9	7.3	11.5
	N	5	5	5	5
ALP	MEAN	78	91	86	70
U/l	ST.DEV	17	21	48	19
	N	5	5	5	5
Total protein	MEAN	62.8	64.4	64.3	61.5
g/l	ST.DEV	2.3	2.9	1.6	1.2
	N	5	5	5	5
Albumin	MEAN	30.6	31.3	32.2 *	31.7
g/l	ST.DEV	0.6	1.1	0.9	0.6
	N	5	5	5	5
Total bilirubin	MEAN	2.6	2.3	3.0	3.0
umol/l	ST.DEV	0.2	0.3	0.5	0.7
	N	5	5	5	5
Urea	MEAN	7.5	7.3	6.5	7.0
mmol/l	ST.DEV	0.5	1.0	1.4	0.5
	N	5	5	5	5
Creatinine	MEAN	42.9	42.3	43.9	42.0
umol/l	ST.DEV	2.5	4.2	1.8	2.0
	N	5	5	5	5
Glucose	MEAN	7.54	7.04	7.40	7.04
mmol/l	ST.DEV	1.15	1.16	1.32	0.45
	N	5	5	5	5
Cholesterol	MEAN	1.55	1.56	1.42	1.27
mmol/l	ST.DEV	0.13	0.38	0.32	0.29
	N	5	5	5	5
Sodium	MEAN	137.8	138.3	137.6	137.2
mmol/l	ST.DEV	1.1	1.5	1.4	1.3
	N	5	5	5	5
Potassium	MEAN	3.78	3.66	3.31	3.85
mmol/l	ST.DEV	0.27	0.65	0.39	0.12
	N	5	5	5	5
Chloride	MEAN	100	99	98	100
mmol/l	ST.DEV	1	1	2	1
	N	5	5	5	5
Calcium	MEAN	2.58	2.58	2.63	2.73 **
mmol/l	ST.DEV	0.06	0.05	0.08	0.08
	N	5	5	5	5
Inorg.Phos	MEAN	1.87	2.00	1.96	2.11
mmol/l	ST.DEV	0.20	0.26	0.28	0.30
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

MACROSCOPIC FINDINGS SUMMARY
MALES

	GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT				
Animals examined	10	10	10	10
Animals without findings	8	8	9	5
Animals affected	2	2	1	5
Liver				
Discolouration	0	0	0	5 #
Kidneys				
Pelvic dilation	1	0	0	0
Seminal vesicles				
Reduced in size	0	1	1	0
Bone				
Tail apex: bent.	1	1	0	0

FEMALES

	GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
INTERCURRENT DEATH				
Animals examined		1		1
Animals without findings		0		1
Animals affected		1		0
Stomach				
Contents:		1		0
END OF TREATMENT				
Animals examined	10	9	10	9
Animals without findings	8	6	9	4
Animals affected	2	3	1	5
Lungs				
Focus/foci	0	0	0	4 #
Liver				
Diaphragmatic hernia	0	0	1	0
Uterus				
Enlarged	0	1	0	0
Contains fluid	0	1	0	0
Cervix				
Enlarged	0	1	0	0
Adrenal glands				
Enlarged	0	1	0	0
Mandibular l.node				
Discolouration	2	0	0	1
Skin				
Alopecia	0	1	0	0

/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level

ORGAN WEIGHTS (GRAM) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
BODY W.	MEAN	424	416	416	403
(GRAM)	ST.DEV	24	24	33	15
	N	10	10	10	10
BRAIN	MEAN	2.04	2.14	2.09	2.09
(GRAM)	ST.DEV	0.10	0.07	0.11	0.03
	N	5	5	5	5
HEART	MEAN	1.263	1.322	1.348	1.416 *
(GRAM)	ST.DEV	0.077	0.070	0.133	0.032
	N	5	5	5	5
LIVER	MEAN	11.47	10.42	10.93	12.46
(GRAM)	ST.DEV	1.18	0.36	1.53	0.59
	N	5	5	5	5
THYMUS	MEAN	0.467	0.352	0.379	0.285 *
(GRAM)	ST.DEV	0.113	0.066	0.120	0.043
	N	5	5	5	5
KIDNEYS	MEAN	3.15	3.13	3.09	3.15
(GRAM)	ST.DEV	0.26	0.25	0.33	0.21
	N	5	5	5	5
ADRENALS	MEAN	0.067	0.070	0.070	0.078
(GRAM)	ST.DEV	0.014	0.011	0.009	0.010
	N	5	5	5	5
SPLEEN	MEAN	1.080	0.924	1.023	0.889
(GRAM)	ST.DEV	0.186	0.106	0.154	0.078
	N	5	5	5	5
TESTES	MEAN	4.04	3.69 *	3.84	4.00
(GRAM)	ST.DEV	0.29	0.29	0.28	0.30
	N	10	10	10	10
EPIDIDYMIDES	MEAN	1.250	1.227	1.169	1.036 **
(GRAM)	ST.DEV	0.122	0.095	0.051	0.094
	N	10	10	10	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
MALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
BODY W.	MEAN	424	416	416	403
(GRAM)	ST.DEV	24	24	33	15
	N	10	10	10	10
BRAIN	MEAN	0.47	0.52	0.50	0.53 *
(%)	ST.DEV	0.02	0.03	0.05	0.02
	N	5	5	5	5
HEART	MEAN	0.292	0.324 *	0.322 *	0.355 **
(%)	ST.DEV	0.017	0.023	0.011	0.017
	N	5	5	5	5
LIVER	MEAN	2.65	2.55	2.60	3.13 **
(%)	ST.DEV	0.16	0.10	0.18	0.23
	N	5	5	5	5
THYMUS	MEAN	0.108	0.086	0.089	0.072 *
(%)	ST.DEV	0.023	0.018	0.022	0.011
	N	5	5	5	5
KIDNEYS	MEAN	0.73	0.77	0.74	0.79
(%)	ST.DEV	0.06	0.06	0.05	0.04
	N	5	5	5	5
ADRENALS	MEAN	0.016	0.017	0.017	0.020
(%)	ST.DEV	0.003	0.002	0.003	0.002
	N	5	5	5	5
SPLEEN	MEAN	0.249	0.227	0.243	0.223
(%)	ST.DEV	0.038	0.031	0.018	0.015
	N	5	5	5	5
TESTES	MEAN	0.96	0.89	0.93	0.99
(%)	ST.DEV	0.09	0.08	0.07	0.06
	N	10	10	10	10
EPIDIDYMIDES	MEAN	0.296	0.295	0.282	0.257 **
(%)	ST.DEV	0.036	0.025	0.016	0.023
	N	10	10	10	10

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN WEIGHTS (GRAM) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
BODY W.	MEAN	268	286	283	271
(GRAM)	ST.DEV	14	13	14	17
	N	5	5	5	5
BRAIN	MEAN	1.91	1.91	1.89	1.84
(GRAM)	ST.DEV	0.06	0.06	0.08	0.06
	N	5	5	5	5
HEART	MEAN	0.950	1.005	1.013	1.049 *
(GRAM)	ST.DEV	0.059	0.061	0.053	0.065
	N	5	5	5	5
LIVER	MEAN	9.22	10.23 *	9.85	9.27
(GRAM)	ST.DEV	0.38	0.41	0.76	0.58
	N	5	5	5	5
THYMUS	MEAN	0.228	0.226	0.201	0.158 *
(GRAM)	ST.DEV	0.048	0.059	0.016	0.027
	N	5	5	5	5
KIDNEYS	MEAN	2.01	2.15	2.26	2.37 **
(GRAM)	ST.DEV	0.15	0.19	0.11	0.18
	N	5	5	5	5
ADRENALS	MEAN	0.093	0.108	0.114 *	0.113 *
(GRAM)	ST.DEV	0.008	0.014	0.009	0.008
	N	5	5	5	5
SPLEEN	MEAN	0.885	0.876	0.870	0.691
(GRAM)	ST.DEV	0.040	0.105	0.213	0.118
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

ORGAN/BODY WEIGHT RATIOS (%) SUMMARY
FEMALES

		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
END OF TREATMENT					
BODY W.	MEAN	268	286	283	271
(GRAM)	ST.DEV	14	13	14	17
	N	5	5	5	5
BRAIN	MEAN	0.71	0.67	0.67	0.68
(%)	ST.DEV	0.06	0.03	0.02	0.03
	N	5	5	5	5
HEART	MEAN	0.355	0.353	0.358	0.388
(%)	ST.DEV	0.026	0.027	0.027	0.028
	N	5	5	5	5
LIVER	MEAN	3.45	3.58	3.48	3.43
(%)	ST.DEV	0.25	0.04	0.31	0.24
	N	5	5	5	5
THYMUS	MEAN	0.085	0.079	0.071	0.058 *
(%)	ST.DEV	0.016	0.018	0.005	0.009
	N	5	5	5	5
KIDNEYS	MEAN	0.75	0.75	0.80	0.88 *
(%)	ST.DEV	0.07	0.07	0.03	0.04
	N	5	5	5	5
ADRENALS	MEAN	0.035	0.038	0.040	0.042
(%)	ST.DEV	0.004	0.004	0.004	0.006
	N	5	5	5	5
SPLEEN	MEAN	0.331	0.306	0.309	0.255
(%)	ST.DEV	0.030	0.025	0.083	0.033
	N	5	5	5	5

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

REPRODUCTION PROCESSES
FEMALES
F0-GENERATION - POST COITUM

FEMALE NUMBER	NOTE	MALE NUMBER	MATING DATE	PREGNANT	SCHEDULE	DELIVERY RECORDED	NECROPSY DATE
GROUP 1 (CONTROL)							
41		1	26JAN2007	YES	BREEDING	17FEB2007	22FEB2007
42		2	26JAN2007	YES	BREEDING	16FEB2007	21FEB2007
43		3	24JAN2007	YES	BREEDING	14FEB2007	19FEB2007
44		4	25JAN2007	YES	BREEDING	15FEB2007	20FEB2007
45		5	26JAN2007	YES	BREEDING	15FEB2007	20FEB2007
46		6	23JAN2007	YES	BREEDING	14FEB2007	19FEB2007
47		7	24JAN2007	YES	BREEDING	15FEB2007	20FEB2007
48		8	25JAN2007	YES	BREEDING	14FEB2007	20FEB2007
49		9	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
50		10	<**>	NO	---	---	21FEB2007
GROUP 2 (50 MG/KG)							
51		11	<**>	NO	---	---	21FEB2007
52		12	26JAN2007	YES	BREEDING	17FEB2007	22FEB2007
53		13	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
54		14	25JAN2007	YES	BREEDING	15FEB2007	20FEB2007
55	$	15	<**>	NO	---	---	21FEB2007
56		16	26JAN2007	YES	BREEDING	17FEB2007	22FEB2007
57		17	26JAN2007	YES	BREEDING	17FEB2007	22FEB2007
58		18	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
59		19	25JAN2007	YES	BREEDING	15FEB2007	20FEB2007
60		20	23JAN2007	YES	BREEDING	14FEB2007	15FEB2007
GROUP 3 (150 MG/KG)							
61		21	26JAN2007	YES	BREEDING	17FEB2007	22FEB2007
62		22	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
63		23	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
64		24	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
65		25	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
66		26	27JAN2007	YES	BREEDING	16FEB2007	21FEB2007
67		27	26JAN2007	YES	BREEDING	16FEB2007	21FEB2007
68		28	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
69		29	23JAN2007	YES	BREEDING	13FEB2007	19FEB2007
70		30	25JAN2007	YES	BREEDING	15FEB2007	20FEB2007
GROUP 4 (500 MG/KG)							
71		31	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
72		32	24JAN2007	YES	BREEDING	15FEB2007	20FEB2007
73		33	<**>	NO	---	---	21FEB2007
74		34	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
75 <IO>		35	26JAN2007	YES	---	---	21FEB2007
76		36	25JAN2007	YES	BREEDING	16FEB2007	21FEB2007
77 <IO>		37	23JAN2007	YES	---	---	21FEB2007
78		38	24JAN2007	YES	BREEDING	15FEB2007	20FEB2007
79		39	25JAN2007	YES	BREEDING	15FEB2007	20FEB2007
80		40	24JAN2007	YES	BREEDING	15FEB2007	20FEB2007

<IO> Implantation sites only
$ Mating not confirmed but showed to be pregnant at necropsy
<**> No mating

MATING PERFORMANCE
F0-GENERATION - POST COITUM

DAY OF THE PAIRING PERIOD	GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
NUMBER OF FEMALES MATED DURING THE FIRST PAIRING PERIOD				
1	1	3	4	1
2	2	-	-	3
3	3	2	3	4
4	3	3	2	1
5	-	-	1	-
MEDIAN PRECOITAL TIME	3	3	3	3
MEAN PRECOITAL TIME	2.9	2.6	2.6	2.6
N	9	8	10	9

+/++ Steel-test significant at 5% (+) or 1% (++) level

BREEDING DATA PER GROUP
F0-GENERATION - LACTATION

	GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
LITTERS				
TOTAL	9	8	10	7
DURATION OF GESTATION				
MEAN (+)	21.2	21.5	21.2	21.9
ST.DEV.	0.8	0.5	0.6	0.4
N	9	8	10	7
DEAD PUPS AT FIRST LITTER CHECK				
LITTERS AFFECTED (#)	2	1	1	1
TOTAL	2	1	3	3
MEAN (+)	0.2	0.1	0.3	0.4
ST.DEV.	0.4	0.4	0.9	1.1
N	9	8	10	7
LIVING PUPS AT FIRST LITTER CHECK				
% OF MALES / FEMALES (#)	45 / 55	43 / 58	49 / 51	48 / 52
TOTAL	144	120	167	48
MEAN (+)	16.0	15.0	16.7	6.9 ++
ST.DEV.	1.7	3.6	2.0	3.0
N	9	8	10	7
POSTNATAL LOSS				
% OF LIVING PUPS	0.0	12.5	6.0	20.8
LITTERS AFFECTED (#)	0	3	5	2
TOTAL (#)	0	15 ##	10 ##	10 ##
MEAN (+)	0.0	1.9	1.0	1.4
ST.DEV.	0.0	4.5	1.3	3.0
N	9	8	10	7
VIABILITY INDEX (#)	100.0	87.5 ##	94.0 ##	79.2 ##

Viability index = (Number of alive pups before planned necropsy / Number of pups born alive) *100
+/++ Steel-test significant at 5% (+) or 1% (++) level
/ ## Fisher's Exact test significant at 5% (#) or 1% (##) level

MEAN BODY WEIGHTS OF PUPS PER GROUP (GRAM)
F0-GENERATION - LACTATION

DAY	SEX		GROUP 1 CONTROL	GROUP 2 50 MG/KG	GROUP 3 150 MG/KG	GROUP 4 500 MG/KG
1	M	MEAN	6.6	6.7	6.3	6.7
		ST.DEV.	0.5	0.6	0.3	0.8
		N	9	8	10	6
	F	MEAN	6.2	6.5	5.9	6.3
		ST.DEV.	0.6	0.7	0.2	0.7
		N	9	8	10	7
	M+F	MEAN	6.4	6.6	6.1	6.4
		ST.DEV.	0.5	0.6	0.3	0.7
		N	9	8	10	7
4	M	MEAN	9.5	10.2	9.1	10.0
		ST.DEV.	1.1	1.4	0.8	1.3
		N	9	7	10	6
	F	MEAN	8.9	9.5	8.3	9.6
		ST.DEV.	1.3	1.7	0.8	1.2
		N	9	7	10	6
	M+F	MEAN	9.2	9.8	8.7	9.7
		ST.DEV.	1.2	1.5	0.8	1.0
		N	9	7	10	6

*/** Dunnett-test based on pooled variance significant at 5% (*) or 1% (**) level

APPENDIX 2 INDIVIDUAL TABLES

MORTALITY DATA
MALES

ANIMAL	SCHEDULED SACRIFICE	OTHER	TREATMENT FROM	TO
GROUP 1 (CONTROL)				
1	08FEB07		08JAN07	07FEB07
2	08FEB07		08JAN07	07FEB07
3	08FEB07		08JAN07	07FEB07
4	08FEB07		08JAN07	07FEB07
5	08FEB07		08JAN07	07FEB07
6	08FEB07		08JAN07	07FEB07
7	08FEB07		08JAN07	07FEB07
8	08FEB07		08JAN07	07FEB07
9	08FEB07		08JAN07	07FEB07
10	08FEB07		08JAN07	07FEB07
GROUP 2 (50 MG/KG)				
11	08FEB07		08JAN07	07FEB07
12	08FEB07		08JAN07	07FEB07
13	08FEB07		08JAN07	07FEB07
14	08FEB07		08JAN07	07FEB07
15	08FEB07		08JAN07	07FEB07
16	08FEB07		08JAN07	07FEB07
17	08FEB07		08JAN07	07FEB07
18	08FEB07		08JAN07	07FEB07
19	08FEB07		08JAN07	07FEB07
20	08FEB07		08JAN07	07FEB07
GROUP 3 (150 MG/KG)				
21	08FEB07		08JAN07	07FEB07
22	08FEB07		08JAN07	07FEB07
23	08FEB07		08JAN07	07FEB07
24	08FEB07		08JAN07	07FEB07
25	08FEB07		08JAN07	07FEB07
26	08FEB07		08JAN07	07FEB07
27	08FEB07		08JAN07	07FEB07
28	08FEB07		08JAN07	07FEB07
29	08FEB07		08JAN07	07FEB07
30	08FEB07		08JAN07	07FEB07
GROUP 4 (500 MG/KG)				
31	08FEB07		08JAN07	07FEB07
32	08FEB07		08JAN07	07FEB07
33	08FEB07		08JAN07	07FEB07
34	08FEB07		08JAN07	07FEB07
35	08FEB07		08JAN07	07FEB07
36	08FEB07		08JAN07	07FEB07
37	08FEB07		08JAN07	07FEB07
38	08FEB07		08JAN07	07FEB07
39	08FEB07		08JAN07	07FEB07
40	08FEB07		08JAN07	07FEB07

MORTALITY DATA
FEMALES

ANIMAL	SCHEDULED SACRIFICE	OTHER	TREATMENT FROM	TO
GROUP 1 (CONTROL)				
41	22FEB07		08JAN07	21FEB07
42	21FEB07		08JAN07	20FEB07
43	19FEB07		08JAN07	18FEB07
44	20FEB07		08JAN07	19FEB07
45	20FEB07		08JAN07	19FEB07
46	19FEB07		08JAN07	18FEB07
47	20FEB07		08JAN07	19FEB07
48	20FEB07		08JAN07	19FEB07
49	21FEB07		08JAN07	20FEB07
50	21FEB07		08JAN07	21FEB07
GROUP 2 (50 MG/KG)				
51	21FEB07		08JAN07	21FEB07
52	22FEB07		08JAN07	21FEB07
53	19FEB07		08JAN07	18FEB07
54	20FEB07		08JAN07	19FEB07
55	21FEB07		08JAN07	21FEB07
56	22FEB07		08JAN07	21FEB07
57	22FEB07		08JAN07	21FEB07
58	19FEB07		08JAN07	18FEB07
59	20FEB07		08JAN07	19FEB07
60		15FEB07	08JAN07	15FEB07
GROUP 3 (150 MG/KG)				
61	22FEB07		08JAN07	21FEB07
62	19FEB07		08JAN07	18FEB07
63	21FEB07		08JAN07	20FEB07
64	19FEB07		08JAN07	18FEB07
65	19FEB07		08JAN07	18FEB07
66	21FEB07		08JAN07	20FEB07
67	21FEB07		08JAN07	20FEB07
68	21FEB07		08JAN07	20FEB07
69	19FEB07		08JAN07	18FEB07
70	20FEB07		08JAN07	19FEB07
GROUP 4 (500 MG/KG)				
71	21FEB07		08JAN07	20FEB07
72	20FEB07		08JAN07	19FEB07
73	21FEB07		08JAN07	21FEB07
74	21FEB07		08JAN07	20FEB07
75	21FEB07		08JAN07	21FEB07
76	21FEB07		08JAN07	20FEB07
77	21FEB07		08JAN07	21FEB07
78	20FEB07		08JAN07	19FEB07
79		17FEB07	08JAN07	17FEB07
80	20FEB07		08JAN07	19FEB07

CLINICAL SIGNS
MALES

		PRE MATING	REPRO PHASE
SIGN (MAX. GRADE)	WEEK:	1.	1. 4.
(LOCATION)	DAY:	1234567123456712345671234567123456712345671234567123	

GROUP 1 (CONTROL)

ANIMAL 1
Secretion / excretion
Chromodacryorrhoea (3) (Eye right) G: 1
ANIMAL 2
No clinical signs noted
ANIMAL 3
No clinical signs noted
ANIMAL 4
No clinical signs noted
ANIMAL 5
Skin / fur / plumage
Scabs (3) (Ear right) G: .....1111111.....
ANIMAL 6
Various
Broken (1) (Tail apex) G: .11111111111111111111111111111111
ANIMAL 7
No clinical signs noted
ANIMAL 8
No clinical signs noted
ANIMAL 9
No clinical signs noted
ANIMAL 10
No clinical signs noted

GROUP 2 (50 MG/KG)

ANIMAL 11
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
ANIMAL 12
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
ANIMAL 13
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
ANIMAL 14
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
ANIMAL 15
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
Various
Broken (1) (Tail apex) G: .11111111111111111111111111111111
ANIMAL 16
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111
ANIMAL 17
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 11111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE WEEK: 1 . . . . . 1 . . . . . 4 . . . . . DAY: 123456712345671234567123456712345671234567123
GROUP 2 (50 MG/KG)		
ANIMAL 18		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111
ANIMAL 19		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111
ANIMAL 20		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111
GROUP 3 (150 MG/KG)		
ANIMAL 21		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 22		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
Secretion / excretion		
Diarrhoea (1)	G:	. . . . . 1 . . . . .
ANIMAL 23		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 24		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 25		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 26		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 27		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 28		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 29		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111
ANIMAL 30		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
MALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE WEEK: 1 . . . . . 1 . . . . . 4 . . . . . DAY: 123456712345671234567123456712345671234567123
GROUP 4 (500 MG/KG)		
ANIMAL 31		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111
ANIMAL 32		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111
ANIMAL 33		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111111
ANIMAL 34		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1112111111111111111
ANIMAL 35		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111
ANIMAL 36		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111111
ANIMAL 37		
Breathing		
Rales (3)	G:	. . . . . 1 . . . . .
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111111
ANIMAL 38		
Breathing		
Rales (3)	G:	. . . . . 1 . . . . .
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	. . . . . 1 1112111111111111
ANIMAL 39		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 1111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
MALES

		PRE MATING	REPRO PHASE
SIGN (MAX. GRADE)	WEEK:	1.	1. . . . . 4. . . . .
(LOCATION)	DAY:	1234567123456712345671234567123456712345671234567123	

GROUP 4 (500 MG/KG)
ANIMAL 40
Skin / fur / plumage
Yellow discolouration (1) (Urine) G: 1111111111111111111111111111111
Secretion / excretion
Salivation (3) G: 11111111111111111

FEMALES

		PRE MATING	REPRO PHASE
SIGN (MAX. GRADE)	WEEK:	1.	1. . . . . 4. . . . .
(LOCATION)	DAY:	1234567123456712345671234567123456712345671234567123	

GROUP 1 (CONTROL)
ANIMAL 41
No clinical signs noted
ANIMAL 42
No clinical signs noted
ANIMAL 43
No clinical signs noted
ANIMAL 44
Skin / fur / plumage
Alopecia (3) (Chest) G: 1
Alopecia (3) (Foreleg right) G: 1
ANIMAL 45
No clinical signs noted
ANIMAL 46
No clinical signs noted
ANIMAL 47
No clinical signs noted
ANIMAL 48
Skin / fur / plumage
Alopecia (3) (Hindleg right) G: . . . . . 1111222222. .
Alopecia (3) (Forelegs) G: 122233333333
Alopecia (3) (Hindlegs) G: 22
ANIMAL 49
No clinical signs noted
ANIMAL 50
No clinical signs noted

GROUP 2 (50 MG/KG)
ANIMAL 51
Skin / fur / plumage
Alopecia (3) (Neck) G: . . . . . 1111111. . . . . .
Scabs (3) (Neck) G: . . . . . 11. . . . . .
Yellow discolouration (1) (Urine) G: 111111111111111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE WEEK: 1 . . . . . 1 . . . . . 4 . . . . . DAY: 12345671234567123456712345671234567123456712345671234567123
GROUP 2 (50 MG/KG)		
ANIMAL 52		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111111
ANIMAL 53		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 111111111111111111111111111
ANIMAL 54		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111
ANIMAL 55		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111111
ANIMAL 56		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	. . . . . 1111. . . .
ANIMAL 57		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111111
ANIMAL 58		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 111111111111111111111111111
ANIMAL 59		
Skin / fur / plumage		
Alopecia (3) (Thigh hind right)	G:	1111111111111111111111111111111111111111
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111111
ANIMAL 60		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	 1111111111111111111111111
GROUP 3 (150 MG/KG)		
ANIMAL 61		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 1111111111111111111111111111111111111111
ANIMAL 62		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 1111111111111111111111111111111111111
ANIMAL 63		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 1111111111111111111111111111111111111
ANIMAL 64		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 1111111111111111111111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE WEEK: 1 . . . . . 1 . . . . . 4 . . . . . DAY: 123456712345671234567123456712345671234567123
GROUP 3 (150 MG/KG)		
ANIMAL 65		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
ANIMAL 66		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
ANIMAL 67		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
ANIMAL 68		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
ANIMAL 69		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
ANIMAL 70		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. . . 11111111111111111111111111111111111111
GROUP 4 (500 MG/KG)		
ANIMAL 71		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111111111111.
Secretion / excretion		
Salivation (3)	G:	. . . . . 11111111111111111111111111111111111.
ANIMAL 72		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	. . . 111. 1. 11111111111111111111111111111111
ANIMAL 73		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 11112221121111111111111111111111111111
ANIMAL 74		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111111111111.
Secretion / excretion		
Salivation (3)	G:	. . . 11112212221111111111111111111111111111.
ANIMAL 75		
Skin / fur / plumage		
Yellow discolouration (1) (Urine)	G:	. 11111111111111111111111111111111111111
Secretion / excretion		
Salivation (3)	G:	 11111111111111111111111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

CLINICAL SIGNS
FEMALES

SIGN (MAX. GRADE) (LOCATION)		PRE MATING / REPRO PHASE WEEK: 1 DAY: 1234567	1 1234567	4 1234567123
GROUP 4 (500 MG/KG)				
ANIMAL 76				
Skin / fur / plumage				
Yellow discolouration (1) (Urine)	G:	.	1111111111111	1111111111111111111.
Secretion / excretion				
Salivation (3)	G:	.....	1111111	2111111111111111111.
ANIMAL 77				
Skin / fur / plumage				
Yellow discolouration (1) (Urine)	G:	.	1111111111111	1111111111111111111
Secretion / excretion				
Salivation (3)	G:	.....	1. 1111111	21211111111111111111
ANIMAL 78				
Skin / fur / plumage				
Yellow discolouration (1) (Urine)	G:	.	1111111111111	1111111111111111111
Secretion / excretion				
Salivation (3)	G:	...	111.. 11111	1111111111111111111
ANIMAL 79				
Skin / fur / plumage				
Piloerection (1)	G:	.....	.....	11. 11111
Yellow discolouration (1) (Urine)	G:	.	1111111111111	1111111111111111111
Secretion / excretion				
Salivation (3)	G:	.....	1111112	1111111111111111111
ANIMAL 80				
Skin / fur / plumage				
Yellow discolouration (1) (Urine)	G:	.	1111111111111	1111111111111111111
Secretion / excretion				
Salivation (3)	G:	.....	1111111	1111111111111111111

G: Highest daily grades
.: Observation performed, sign not present

BODY WEIGHTS (GRAM)
MALES

	PRE MATING		MATING PERIOD					
DAYS	1	8	1	8	15	22	29	36
WEEKS	1	2	1	2	3	4	5	6
ANIMAL								
GROUP 1 (CONTROL)								
1	334	376	420	445	471			
2	329	359	395	413	434			
3	333	380	418	447	474			
4	327	362	396	419	431			
5	331	369	395	428	445			
6	340	382	414	441	458			
7	333	377	419	445	477			
8	326	360	382	404	413			
9	328	353	377	389	405			
10	366	403	425	440	467			
GROUP 2 (50 MG/KG)								
11	344	372	423	451	471			
12	338	363	405	418	429			
13	333	367	388	409	428			
14	331	362	405	429	439			
15	327	349	381	389	402			
16	335	357	387	393	421			
17	352	378	407	420	444			
18	321	355	379	410	428			
19	328	363	402	419	448			
20	345	391	429	449	474			
GROUP 3 (150 MG/KG)								
21	327	362	394	412	434			
22	342	384	427	453	486			
23	347	357	371	378	397			
24	349	368	388	403	421			
25	343	383	431	462	492			
26	341	371	397	408	429			
27	338	388	423	445	478			
28	341	374	411	432	446			
29	327	374	385	398	424			
30	323	354	378	395	417			
GROUP 4 (500 MG/KG)								
31	349	366	406	402	433			
32	351	373	405	408	433			
33	328	350	389	419	449			
34	327	340	383	395	421			
35	335	350	377	374	410			
36	326	346	374	389	413			
37	349	365	393	403	423			
38	339	361	420	406	437			
39	332	360	402	384	417			
40	355	389	420	440	467			

BODY WEIGHTS (GRAM)
FEMALES

	PRE MATING		MATING PERIOD					
DAYS	1	8	1	8	15	22	29	36
WEEKS	1	2	1	2	3	4	5	6
ANIMAL								
GROUP 1 (CONTROL)								
41	239	251	254	---	---	---	---	
42	239	244	237	---	---	---	---	
43	231	240	254	288	312	387	---	
44	220	230	230	---	---	---	---	
45	223	242	248	261	292	368	---	
46	218	224	242	---	---	---	---	
47	221	230	248	---	---	---	---	
48	234	252	258	---	---	---	---	
49	226	236	247	---	---	---	---	
50	228	242	248	279	274	283	292	
GROUP 2 (50 MG/KG)								
51	223	241	229	265	273	306	303	
52	234	239	240	---	---	---	---	
53	241	242	259	---	---	---	---	
54	220	236	244	---	---	---	---	
55	236	248	244	289	283	319	361	
56	216	229	224	---	---	---	---	
57	233	244	241	---	---	---	---	
58	231	232	247	---	---	---	---	
59	229	241	260	280	326	419	---	
60	235	235	269	---	---	---	---	
GROUP 3 (150 MG/KG)								
61	212	218	218					
62	240	241	264					
63	240	247	255					
64	228	230	249					
65	216	223	232					
66	229	237	239					
67	224	235	247					
68	219	233	240					
69	233	232	246					
70	246	262	272					
GROUP 4 (500 MG/KG)								
71	237	253	257	---	---	---	---	
72	224	234	252	---	---	---	---	
73	238	240	243	265	268	295	296	
74	238	250	259	---	---	---	---	
75	229	234	233	---	---	---	---	
76	230	234	233	---	---	---	---	
77	245	236	258	---	---	---	---	
78	221	225	237	---	---	---	---	
79	218	231	244	265	296	336	---	
80	214	228	248	---	---	---	---	

BODY WEIGHTS (GRAM)
FEMALES
F0-GENERATION

	POST COITUM							LACTATION	
DAYS	0	4	7	11	14	17	20	1	4
ANIMAL									
GROUP 1 (CONTROL)									
41	271	289	304	330	341	387	454	332	333
42	239	260	273	298	310	357	418	292	302
43	---	---	---	---	---	---	---	307	330
44	241	265	280	291	323	357	401	284	303
45	---	---	---	---	---	---	---	306	313
46	238	269	274	296	309	352	410	307	331
47	250	270	276	295	312	351	403	303	320
48	266	278	287	310	335	386	437	327	325
49	246	269	282	292	317	352	405	294	324
GROUP 2 (50 MG/KG)									
52	257	281	286	298	323	365	415	321	329
53	258	299	313	338	363	412	473	374	350
54	247	265	276	291	317	367	425	313	326
56	235	255	266	288	306	327	348	298	293
57	251	264	275	306	315	366	418	303	332
58	241	264	269	295	310	355	416	305	318
59	---	---	---	---	---	---	---	330	347
60	265	287	299	321	342	374	432	350	---
GROUP 3 (150 MG/KG)									
61	230	245	258	273	287	329	380	265	278
62	250	279	282	305	316	347	396	332	328
63	251	275	282	303	330	362	427	300	315
64	243	263	282	312	322	356	429	306	339
65	231	241	248	244	270	309	357	273	276
66	248	263	269	295	314	368	418	304	323
67	261	271	276	308	325	370	424	338	325
68	240	254	273	288	315	353	417	290	313
69	246	265	264	281	296	340	392	282	306
70	281	292	298	316	342	387	447	322	338
GROUP 4 (500 MG/KG)									
71	248	272	292	307	314	338	354	291	308
72	258	278	291	327	332	355	386	312	307
74	264	286	300	316	336	355	398	322	323
75 <IO>	253	266	275	287	297	312	327	---	---
76	244	251	260	276	282	308	343	278	294
77 <IO>	253	271	283	306	319	334	356	---	---
78	238	246	253	273	284	316	357	270	273
79	---	---	---	---	---	---	---	301	295
80	251	258	270	304	298	330	368	300	316

<IO> Implantation sites only

BODY WEIGHT GAIN (%)
MALES

	PRE MATING		MATING PERIOD					
DAYS	1	8	1	8	15	22	29	36
WEEKS	1	2	1	2	3	4	5	6
ANIMAL								
GROUP 1 (CONTROL)								
1	0	13	26	33	41			
2	0	9	20	26	32			
3	0	14	26	34	42			
4	0	11	21	28	32			
5	0	11	19	29	34			
6	0	12	22	30	35			
7	0	13	26	34	43			
8	0	10	17	24	27			
9	0	8	15	19	23			
10	0	10	16	20	28			
GROUP 2 (50 MG/KG)								
11	0	8	23	31	37			
12	0	7	20	24	27			
13	0	10	17	23	29			
14	0	9	22	30	33			
15	0	7	17	19	23			
16	0	7	16	17	26			
17	0	7	16	19	26			
18	0	11	18	28	33			
19	0	11	23	28	37			
20	0	13	24	30	37			
GROUP 3 (150 MG/KG)								
21	0	11	20	26	33			
22	0	12	25	32	42			
23	0	3	7	9	14			
24	0	5	11	15	21			
25	0	12	26	35	43			
26	0	9	16	20	26			
27	0	15	25	32	41			
28	0	10	21	27	31			
29	0	14	18	22	30			
30	0	10	17	22	29			
GROUP 4 (500 MG/KG)								
31	0	5	16	15	24			
32	0	6	15	16	23			
33	0	7	19	28	37			
34	0	4	17	21	29			
35	0	4	13	12	22			
36	0	6	15	19	27			
37	0	5	13	15	21			
38	0	6	24	20	29			
39	0	8	21	16	26			
40	0	10	18	24	32			

BODY WEIGHT GAIN (%)
FEMALES

	PRE MATING		MATING PERIOD					
DAYS	1	8	1	8	15	22	29	36
WEEKS	1	2	1	2	3	4	5	6
ANIMAL								
GROUP 1 (CONTROL)								
41	0	5	6	---	---	---	---	
42	0	2	-1	---	---	---	---	
43	0	4	10	25	35	68	---	
44	0	5	5	---	---	---	---	
45	0	9	11	17	31	65	---	
46	0	3	11	---	---	---	---	
47	0	4	12	---	---	---	---	
48	0	8	10	---	---	---	---	
49	0	4	9	---	---	---	---	
50	0	6	9	22	20	24	28	
GROUP 2 (50 MG/KG)								
51	0	8	3	19	22	37	36	
52	0	2	3	---	---	---	---	
53	0	0	7	---	---	---	---	
54	0	7	11	---	---	---	---	
55	0	5	3	22	20	35	53	
56	0	6	4	---	---	---	---	
57	0	5	3	---	---	---	---	
58	0	0	7	---	---	---	---	
59	0	5	14	22	42	83	---	
60	0	0	14	---	---	---	---	
GROUP 3 (150 MG/KG)								
61	0	3	3					
62	0	0	10					
63	0	3	6					
64	0	1	9					
65	0	3	7					
66	0	3	4					
67	0	5	10					
68	0	6	10					
69	0	0	6					
70	0	7	11					
GROUP 4 (500 MG/KG)								
71	0	7	8	---	---	---	---	
72	0	4	13	---	---	---	---	
73	0	1	2	11	13	24	24	
74	0	5	9	---	---	---	---	
75	0	2	2	---	---	---	---	
76	0	2	1	---	---	---	---	
77	0	-4	5	---	---	---	---	
78	0	2	7	---	---	---	---	
79	0	6	12	22	36	54	---	
80	0	7	16	---	---	---	---	

BODY WEIGHT GAIN (%)
FEMALES
F0-GENERATION

	POST COITUM							LACTATION	
DAYS	0	4	7	11	14	17	20	1	4
ANIMAL									
GROUP 1 (CONTROL)									
41	0	7	12	22	26	43	68	0	0
42	0	9	14	25	30	49	75	0	3
43	---	---	---	---	---	---	---	0	7
44	0	10	16	21	34	48	66	0	7
45	---	---	---	---	---	---	---	0	2
46	0	13	15	24	30	48	72	0	8
47	0	8	10	18	25	40	61	0	6
48	0	5	8	17	26	45	64	0	-1
49	0	9	15	19	29	43	65	0	10
GROUP 2 (50 MG/KG)									
52	0	9	11	16	26	42	61	0	2
53	0	16	21	31	41	60	83	0	-6
54	0	7	12	18	28	49	72	0	4
56	0	9	13	23	30	39	48	0	-2
57	0	5	10	22	25	46	67	0	10
58	0	10	12	22	29	47	73	0	4
59	---	---	---	---	---	---	---	0	5
60	0	8	13	21	29	41	63	0	---
GROUP 3 (150 MG/KG)									
61	0	7	12	19	25	43	65	0	5
62	0	12	13	22	26	39	58	0	-1
63	0	10	12	21	31	44	70	0	5
64	0	8	16	28	33	47	77	0	11
65	0	4	7	6	17	34	55	0	1
66	0	6	8	19	27	48	69	0	6
67	0	4	6	18	25	42	62	0	-4
68	0	6	14	20	31	47	74	0	8
69	0	8	7	14	20	38	59	0	9
70	0	4	6	12	22	38	59	0	5
GROUP 4 (500 MG/KG)									
71	0	10	18	24	27	36	43	0	6
72	0	8	13	27	29	38	50	0	-2
74	0	8	14	20	27	34	51	0	0
75 <IO>	0	5	9	13	17	23	29	---	---
76	0	3	7	13	16	26	41	0	6
77 <IO>	0	7	12	21	26	32	41	---	---
78	0	3	6	15	19	33	50	0	1
79	---	---	---	---	---	---	---	0	-2
80	0	3	8	21	19	31	47	0	5

<IO> Implantation sites only

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
1	29	30
2	29	30
GROUP 2 (50 MG/KG)		
3	28	29
4	28	29
GROUP 3 (150 MG/KG)		
5	28	30
6	29	30
GROUP 4 (500 MG/KG)		
7	29	32
8	28	33

FEMALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
9	20	20
10	19	20
GROUP 2 (50 MG/KG)		
11	19	20
12	20	20
GROUP 3 (150 MG/KG)		
13	18	19
14	20	21
GROUP 4 (500 MG/KG)		
15	20	23
16	18	21

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES
F0-GENERATION

	POST COITUM						LACTATION
DAYS	0-4	4-7	7-11	11-14	14-17	17-20	1-4
ANIMAL							
GROUP 1 (CONTROL)							
41	28	25	30	31	34	37	39
42	21	22	29	26	39	31	28
43	---	---	---	---	---	---	37
44	25	23	24	34	31	31	33
45	---	---	---	---	---	---	29
46	25	24	22	23	33	35	44
47	26	23	24	29	31	29	40
48	22	22	24	27	32	33	30
49	23	24	24	28	28	29	31
GROUP 2 (50 MG/KG)							
52	24	24	28	30	31	36	44
53	29	29	29	28	34	33	55
54	24	22	26	37	31	34	34
56	20	21	27	29	32	29	28
57	20	19	27	27	32	33	38
58	22	22	23	45	32	36	25
59	---	---	---	---	---	---	56
60	28	26	24	31	34	40	---
GROUP 3 (150 MG/KG)							
61	21	41	23	23	26	26	35
62	25	22	23	24	29	30	78
63	22	21	25	30	26	29	31
64	23	25	27	27	29	34	69
65	21	20	20	22	25	28	46
66	20	18	25	27	32	29	29
67	21	21	27	27	30	33	27
68	21	22	25	27	29	32	27
69	24	22	21	23	32	29	52
70	23	21	25	31	28	30	29
GROUP 4 (500 MG/KG)							
71	22	26	27	28	31	29	19
72	28	30	28	35	34	32	22
74	25	29	28	32	29	38	20
75 <IO>	26	28	27	28	33	32	---
76	19	20	23	25	27	31	23
77 <IO>	38	22	23	27	31	32	---
78	20	21	19	27	30	27	15
79	---	---	---	---	---	---	29
80	24	23	28	31	33	32	31

<IO> Implantation sites only

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
MALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
1	77	82
2	78	79
GROUP 2 (50 MG/KG)		
3	76	81
4	76	79
GROUP 3 (150 MG/KG)		
5	76	80
6	77	80
GROUP 4 (500 MG/KG)		
7	80	89
8	77	89

FEMALES

	PRE MATING	
DAYS	1-8	8-15
WEEKS	1-2	2-3
CAGE		
GROUP 1 (CONTROL)		
9	82	82
10	81	84
GROUP 2 (50 MG/KG)		
11	78	81
12	83	86
GROUP 3 (150 MG/KG)		
13	79	84
14	83	86
GROUP 4 (500 MG/KG)		
15	84	95
16	77	92

RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY)
FEMALES
F0-GENERATION

	POST COITUM						LACTATION
DAYS	0-4	4-7	7-11	11-14	14-17	17-20	1-4
ANIMAL							
GROUP 1 (CONTROL)							
41	95	83	89	90	89	81	118
42	81	81	98	84	108	75	94
43	---	---	---	---	---	---	111
44	92	83	81	104	87	78	110
45	---	---	---	---	---	---	94
46	93	89	75	74	93	85	132
47	96	83	81	93	89	73	126
48	78	75	77	82	82	76	92
49	84	86	83	87	80	72	95
GROUP 2 (50 MG/KG)							
52	86	84	92	94	85	86	133
53	98	94	85	77	83	70	156
54	92	80	88	116	85	79	104
56	79	80	94	95	98	82	96
57	76	70	89	86	88	79	115
58	81	83	76	146	89	87	78
59	---	---	---	---	---	---	162
60	96	87	76	91	90	93	---
GROUP 3 (150 MG/KG)							
61	85	159	82	80	79	69	127
62	88	77	74	77	84	77	238
63	78	76	83	92	73	67	98
64	87	87	87	84	81	80	203
65	87	81	81	81	82	79	165
66	76	67	83	87	88	69	89
67	76	76	87	83	81	78	83
68	84	82	88	86	82	77	87
69	91	82	76	79	95	74	170
70	80	69	78	92	73	68	86
GROUP 4 (500 MG/KG)							
71	79	89	87	88	92	81	61
72	100	102	86	104	97	83	71
74	88	98	89	95	81	95	62
75 <IO>	96	103	93	93	107	99	---
76	77	77	84	90	89	90	79
77 <IO>	141	78	76	85	92	90	---
78	82	82	69	95	95	76	55
79	---	---	---	---	---	---	98
80	93	85	90	105	99	88	97

<IO> Implantation sites only

FUNCTIONAL OBSERVATIONS
MALES
TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 1 (CONTROL)					
1	0	0	0	0	0
2	0	0	0	0	0
4	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
GROUP 2 (50 MG/KG)					
12	0	0	0	0	0
13	0	0	0	0	0
14	0	0	0	0	0
16	0	0	0	0	0
17	0	0	0	0	0
GROUP 3 (150 MG/KG)					
21	0	0	0	0	0
22	0	0	0	0	0
23	0	0	0	0	0
24	0	0	0	0	0
25	0	0	0	0	0
GROUP 4 (500 MG/KG)					
31	0	0	0	0	0
32	0	0	0	0	0
34	0	0	0	0	0
35	0	0	0	0	0
36	0	0	0	0	0

FEMALES
TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 1 (CONTROL)					
42	0	0	0	0	0
44	0	0	0	0	0
45	0	0	0	0	0
47	0	0	0	0	0
48	0	0	0	0	0
GROUP 2 (50 MG/KG)					
52	0	0	0	0	0
53	0	0	0	0	0
54	0	0	0	0	0
58	0	0	0	0	0
59	0	0	0	0	0
GROUP 3 (150 MG/KG)					
62	0	0	0	0	0
63	0	0	0	0	0
64	0	0	0	0	0
66	0	0	0	0	0
70	0	0	0	0	0

FUNCTIONAL OBSERVATIONS
FEMALES
TREATMENT

ANIMAL	HEARING SCORE 0/1	PUPIL L SCORE 0/1	PUPIL R SCORE 0/1	STATIC R SCORE 0/1	GRIP SCORE 0/1
GROUP 4 (500 MG/KG)					
71	0	0	0	0	0
72	0	0	0	0	0
74	0	0	0	0	0
78	0	0	0	0	0
79	0	0	0	0	0
80	0	0	0	0	0

MOTOR ACTIVITY TEST

MALES
WEEK 4

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 1 (CONTROL)														
1	High	375	33	190	135	114	0	115	191	0	35	218	9	1415
1	Low	482	162	613	418	273	53	102	277	49	110	316	142	2997
2	High	159	57	230	229	138	204	106	228	94	121	338	51	1955
2	Low	399	296	439	696	656	541	476	331	241	309	516	243	5143
4	High	162	292	303	216	0	29	235	61	224	1	14	8	1545
4	Low	578	453	625	667	137	118	280	235	703	43	11	19	3869
6	High	66	89	279	189	84	11	341	96	126	239	504	299	2323
6	Low	300	396	499	307	66	141	838	156	249	557	559	328	4396
7	High	203	289	253	80	300	129	415	299	143	418	466	7	3002
7	Low	531	762	701	361	645	92	485	569	335	940	1068	50	6539
GROUP 2 (50 MG/KG)														
12	High	216	218	205	102	155	108	228	4	187	163	135	1	1722
12	Low	418	330	801	370	487	312	390	26	348	409	399	155	4445
13	High	100	8	94	73	6	0	9	2	87	37	20	73	509
13	Low	363	262	465	417	465	95	25	26	234	420	303	111	3186
14	High	92	72	51	126	115	113	0	112	23	220	238	112	1274
14	Low	123	343	393	720	367	592	75	270	382	565	399	414	4643
16	High	138	99	177	495	276	69	386	3	35	107	225	55	2065
16	Low	282	797	482	756	662	234	517	21	148	218	443	305	4865
17	High	297	261	667	465	475	395	1	78	413	388	566	0	4006
17	Low	422	578	498	397	585	456	35	141	379	851	537	57	4936
GROUP 3 (150 MG/KG)														
21	High	131	64	61	275	372	563	115	11	261	199	391	289	2732
21	Low	330	337	256	856	789	783	54	95	137	488	589	556	5270
22	High	273	170	174	674	280	352	547	5	18	69	420	26	3008
22	Low	554	612	476	526	94	289	699	64	64	234	759	123	4494
23	High	248	180	133	35	48	255	304	200	152	249	202	140	2146
23	Low	467	265	237	32	264	612	586	305	144	444	339	562	4257
24	High	155	73	248	480	144	212	360	57	274	220	537	208	2968
24	Low	290	118	932	878	215	160	540	162	639	473	1036	330	5773
25	High	491	490	221	372	12	85	437	174	8	188	727	280	3485
25	Low	711	459	289	673	15	145	433	237	84	210	772	204	4232
GROUP 4 (500 MG/KG)														
31	High	78	0	233	256	237	152	114	238	165	363	283	158	2277
31	Low	256	24	622	507	765	562	425	567	509	740	1263	632	6872
32	High	234	249	269	79	344	143	229	351	10	210	429	72	2619
32	Low	412	390	777	210	1074	1128	311	999	209	527	893	113	7043
34	High	199	27	60	103	270	248	504	17	57	303	244	198	2230
34	Low	229	196	591	642	456	427	506	97	123	465	521	185	4438
35	High	22	152	224	322	175	163	1	120	113	92	201	82	1667
35	Low	168	211	500	536	425	540	62	212	503	484	719	191	4551
36	High	182	66	138	93	254	110	147	178	83	527	446	294	2518
36	Low	657	264	227	356	532	396	280	81	92	396	632	425	4338

MOTOR ACTIVITY TEST

FEMALES
LACTATION

Animal number	Location of sensor	Counts per sample period (hour) 1	2	3	4	5	6	7	8	9	10	11	12	Total
GROUP 1 (CONTROL)														
42	High	4941	681	1676	674	0	1238	1305	45	6	1092	658	499	12815
42	Low	875	371	1021	317	3	910	431	18	63	229	5	244	4487
44	High	146	208	188	123	228	79	103	42	53	30	13	72	1285
44	Low	570	400	710	256	620	320	636	228	127	187	46	120	4220
45	High	19	18	2	192	156	92	136	19	104	27	0	0	765
45	Low	192	229	34	474	195	148	519	328	907	223	44	46	3339
47	High	17	88	136	162	113	0	343	4	1	93	2	0	959
47	Low	70	318	439	1025	447	73	740	0	9	376	37	1	3535
48	High	46	82	0	67	93	2	39	28	19	22	0	0	398
48	Low	403	513	123	450	811	55	599	559	355	233	32	93	4226
GROUP 2 (50 MG/KG)														
52	High	277	4	190	3	127	3	154	118	70	60	322	195	1523
52	Low	628	28	483	8	372	25	412	31	401	42	348	496	3274
53	High	0	30	62	54	94	0	115	0	99	14	101	11	580
53	Low	32	80	329	322	513	7	283	11	378	351	191	136	2633
54	High	107	41	0	161	211	129	2	94	47	0	148	13	953
54	Low	355	276	15	487	446	321	44	393	233	5	432	111	3118
58	High	155	163	186	171	162	156	36	0	198	16	9	47	1299
58	Low	603	702	587	691	530	653	235	7	1017	31	35	291	5382
59	High	83	112	38	138	165	73	77	6	242	8	68	26	1036
59	Low	548	871	259	833	765	400	636	70	1069	38	227	216	5932
GROUP 3 (150 MG/KG)														
62	High	0	67	130	51	101	0	78	112	0	35	140	103	817
62	Low	265	141	481	190	806	4	399	369	1	302	268	676	3902
63	High	1	82	243	58	187	0	165	189	148	78	106	0	1257
63	Low	7	131	643	264	698	95	560	468	296	191	282	1	3636
64	High	2	184	95	0	205	102	5	209	43	30	124	139	1138
64	Low	11	627	277	40	1073	72	32	1177	70	207	499	358	4443
66	High	120	58	333	66	301	55	324	111	13	163	24	169	1737
66	Low	157	7	565	86	807	203	880	244	42	242	15	324	3572
70	High	27	257	5	25	165	22	2	190	54	0	189	12	948
70	Low	171	342	84	167	306	119	5	457	136	19	354	31	2191
GROUP 4 (500 MG/KG)														
71	High	177	67	244	143	242	119	127	66	78	130	57	43	1493
71	Low	534	105	1101	494	1079	454	853	464	348	798	231	37	6498
72	High	319	78	170	123	193	176	57	65	168	133	109	32	1623
72	Low	1625	438	997	747	1186	843	374	256	919	490	507	308	8690
74	High	115	40	153	0	164	111	58	79	0	68	53	22	863
74	Low	1392	405	1849	0	1487	442	1023	835	26	530	502	284	8775
78	High	30	20	39	7	4	177	22	4	166	173	274	0	916
78	Low	117	139	163	47	125	277	141	56	2099	1754	164	0	5082
80	High	780	252	20	25	117	269	645	710	602	1386	1017	723	6546
80	Low	481	485	335	409	1255	771	825	217	501	455	350	337	6421

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
1	6.8	20.6	72.4	4.7	1.6
2	10.7	16.0	78.0	5.0	1.0
4	10.1	10.4	85.1	1.8	2.1
6	10.6	26.0	67.0	5.0	2.0
7	11.0	13.5	81.4	3.2	1.3
GROUP 2 (50 MG/KG)					
12	7.8	15.6	79.9	2.8	1.1
13	9.7	13.1	83.7	1.5	1.2
14	9.4	15.1	81.9	1.4	1.1
16	11.7	9.7	86.5	2.3	1.2
17	12.6	11.8	84.4	2.3	1.2
GROUP 3 (150 MG/KG)					
21	8.7	12.0	85.0	1.7	0.9
22	7.6	13.8	81.1	2.5	2.1
23	8.8	11.9	83.8	2.6	1.4
24	10.2	13.9	81.8	2.8	1.1
25	9.8	13.4	80.1	4.8	1.1
GROUP 4 (500 MG/KG)					
31	10.6	14.7	82.7	1.9	0.3
32	10.3	17.0	78.2	3.6	0.7
34	9.1	14.0	83.4	1.7	0.5
35	12.3	28.3	67.6	3.3	0.4
36	10.7	13.0	80.0	7.0	0.0

MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
1	0.7	8.20	2.9	11.6	9.5
2	0.0	8.61	2.5	12.0	9.4
4	0.5	8.40	2.6	12.3	9.8
6	0.0	8.39	2.5	11.3	9.6
7	0.6	8.42	4.0	12.0	10.2
GROUP 2 (50 MG/KG)					
12	0.6	8.63	2.8	12.3	9.9
13	0.5	7.97	3.8	12.8	9.3
14	0.6	8.36	3.1	13.0	9.3
16	0.3	8.26	3.0	11.6	10.2
17	0.4	8.30	2.8	13.1	8.9
GROUP 3 (150 MG/KG)					
21	0.4	8.45	3.3	12.3	9.7
22	0.5	8.15	3.6	12.1	9.5
23	0.2	9.05	2.4	12.8	9.7
24	0.5	8.78	3.2	13.9	9.4
25	0.5	8.19	3.2	12.2	9.5

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 4 (500 MG/KG)					
31	0.3	8.20	3.6	13.5	9.6
32	0.4	7.87	2.8	12.2	9.2
34	0.4	7.80	3.9	13.7	9.5
35	0.3	8.49	3.3	13.4	9.3
36	0.0	8.22	3.3	12.3	9.9

MALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
1	0.425	51.8	1.16	22.39	1048
2	0.420	48.8	1.09	22.42	747
4	0.443	52.8	1.17	22.17	1127
6	0.437	52.1	1.14	21.93	612
7	0.469	55.7	1.21	21.78	972
GROUP 2 (50 MG/KG)					
12	0.447	51.8	1.14	22.08	1034
13	0.410	51.5	1.17	22.71	904
14	0.419	50.2	1.12	22.29	1174
16	0.447	54.1	1.23	22.73	986
17	0.398	47.9	1.07	22.40	1180
GROUP 3 (150 MG/KG)					
21	0.433	51.2	1.15	22.46	1046
22	0.433	53.0	1.17	21.97	1039
23	0.443	49.0	1.07	21.90	1043
24	0.418	47.6	1.07	22.59	1119
25	0.426	52.1	1.17	22.38	879
GROUP 4 (500 MG/KG)					
31	0.420	51.2	1.17	22.78	799
32	0.408	51.8	1.17	22.50	1310
34	0.418	53.6	1.21	22.62	1047
35	0.423	49.8	1.09	21.98	1062
36	0.442	53.7	1.21	22.45	686

MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
1	17.6	11.5
2	17.8	11.5
4	19.7	14.3
6	17.9	11.1
7	18.2	10.1

HAEMATOLOGY
MALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 2 (50 MG/KG)		
12	16.9	17.1
13	18.4	19.0
14	17.6	18.0
16	17.0	16.0
17	17.7	16.4
GROUP 3 (150 MG/KG)		
21	17.4	11.5
22	18.5	19.1
23	18.6	16.7
24	17.9	17.3
25	17.4	13.8
GROUP 4 (500 MG/KG)		
31	18.6	16.1
32	17.7	15.2
34	18.6	17.4
35	18.2	15.6
36	16.8	10.6

FEMALES
END OF TREATMENT

ANIMAL	WBC 10E9/l	Neutrophils %WBC	Lymphocytes %WBC	Monocytes %WBC	Eosinophils %WBC
GROUP 1 (CONTROL)					
42	3.7	21.6	75.7	2.1	0.4
44	6.8	18.5	77.4	2.7	1.0
45	7.4	24.7	72.3	1.9	0.9
47	10.8	16.9	78.5	2.7	1.4
48	7.6	14.1	83.1	1.5	1.1
GROUP 2 (50 MG/KG)					
52	5.5	18.0	79.0	3.0	0.0
53	3.5	31.0	64.0	5.0	0.0
54	6.4	20.2	76.6	1.5	1.5
58	3.3	21.0	74.0	2.0	3.0
59	6.3	17.2	79.4	2.1	0.9
GROUP 3 (150 MG/KG)					
62	5.1	22.5	74.5	2.4	0.4
63	5.6	30.6	65.0	3.5	0.5
64	2.4	24.4	72.0	2.1	1.2
66	5.8	21.7	74.2	3.1	0.6
70	6.3	16.4	80.9	1.7	0.8
GROUP 4 (500 MG/KG)					
71	5.2	19.6	77.6	2.1	0.3
72	7.8	22.8	73.6	3.1	0.3
74	6.5	46.5	49.5	3.0	0.7
78	4.3	31.8	64.1	3.7	0.2
80	5.0	16.6	79.7	3.3	0.2

HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Basophils %WBC	Red blood cells 10E12/l	Reticulocytes %RBC	RDW %	Haemoglobin mmol/l
GROUP 1 (CONTROL)					
42	0.3	7.24	9.8	17.9	8.2
44	0.4	7.81	5.0	14.6	9.6
45	0.2	7.58	6.2	14.8	9.3
47	0.5	7.95	4.7	14.6	9.6
48	0.2	7.53	4.1	13.3	9.0
GROUP 2 (50 MG/KG)					
52	0.0	7.84	4.3	14.8	8.9
53	0.0	8.00	5.3	16.1	9.3
54	0.2	7.18	5.3	14.8	8.6
58	0.0	7.20	6.9	18.8	8.4
59	0.4	7.25	6.4	16.0	9.4
GROUP 3 (150 MG/KG)					
62	0.2	7.74	4.8	14.5	9.1
63	0.3	7.14	10.5	17.5	8.7
64	0.3	7.05	7.7	17.1	8.6
66	0.3	8.05	7.1	14.3	9.7
70	0.1	7.46	4.2	13.9	8.7
GROUP 4 (500 MG/KG)					
71	0.4	8.03	3.6	12.7	9.4
72	0.2	8.26	3.3	14.0	9.4
74	0.2	6.68	7.3	16.3	8.0
78	0.2	7.22	8.2	17.5	8.8
80	0.3	6.74	7.4	16.0	8.6

FEMALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 1 (CONTROL)					
42	0.381	52.6	1.13	21.54	1460
44	0.420	53.8	1.23	22.88	1323
45	0.417	55.0	1.23	22.31	1499
47	0.426	53.6	1.20	22.45	1418
48	0.401	53.3	1.20	22.52	1011
GROUP 2 (50 MG/KG)					
52	0.389	49.7	1.14	22.95	822
53	0.419	52.4	1.17	22.29	1286
54	0.388	54.1	1.20	22.10	1570
58	0.387	53.7	1.17	21.84	1391
59	0.420	57.9	1.30	22.45	930
GROUP 3 (150 MG/KG)					
62	0.412	53.3	1.18	22.15	1016
63	0.402	56.3	1.22	21.60	1364
64	0.400	56.8	1.22	21.51	1285
66	0.444	55.2	1.20	21.81	1472
70	0.388	52.0	1.16	22.32	2058

HAEMATOLOGY
FEMALES
END OF TREATMENT

ANIMAL	Haematocrit l/l	MCV fl	MCH fmol	MCHC mmol/l	Platelets 10E9/l
GROUP 4 (500 MG/KG)					
71	0.418	52.1	1.17	22.43	1071
72	0.416	50.3	1.14	22.58	1132
74	0.370	55.4	1.19	21.56	1262
78	0.404	55.9	1.22	21.91	1546
80	0.378	56.1	1.28	22.78	1574

FEMALES
END OF TREATMENT

ANIMAL	PT s	APTT s
GROUP 1 (CONTROL)		
42	16.8	17.0
44	17.5	16.7
45	17.7	17.5
47	17.5	20.2
48	17.4	18.6
GROUP 2 (50 MG/KG)		
52	17.8	18.4
53	16.2	14.3
54	17.3	21.8
58	15.6	12.9
59	17.0	16.5
GROUP 3 (150 MG/KG)		
62	17.3	16.1
63	18.6	18.9
64	17.0	19.8
66	16.9	15.0
70	16.5	13.2
GROUP 4 (500 MG/KG)		
71	15.8	13.1
72	18.3	20.1
74	18.7	17.0
78	19.4	22.1
80	18.0	15.0

CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
1	31.4	68.1	97	64.4	32.3
2	42.5	83.3	145	62.9	31.0
4	35.6	71.8	84	58.6	29.7
6	36.7	75.2	86	63.5	30.9
7	41.1	70.9	101	62.1	31.0
GROUP 2 (50 MG/KG)					
12	30.3	75.3	112	63.7	32.0
13	34.5	70.8	101	61.3	30.7
14	36.4	65.8	114	66.9	30.9
16	51.0	77.6	120	63.4	31.5
17	39.8	69.0	110	58.7	30.1
GROUP 3 (150 MG/KG)					
21	43.0	73.0	120	61.4	31.0
22	34.9	74.4	98	61.2	30.0
23	64.8	75.8	115	68.3	33.1
24	48.0	89.3	108	63.5	31.4
25	38.8	81.4	125	62.7	30.4
GROUP 4 (500 MG/KG)					
31	64.2	101.1	158	66.2	32.5
32	62.7	92.0	140	61.1	31.5
34	67.2	88.2	123	58.9	29.5
35	69.8	108.3	182	64.0	30.8
36	63.5	92.8	140	65.3	32.9

MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
1	2.2	6.6	42.1	7.50	1.84
2	2.5	5.9	38.6	7.25	1.38
4	2.5	6.7	39.3	8.48	1.59
6	2.6	5.3	35.8	8.78	1.56
7	2.3	6.6	39.3	8.29	1.24
GROUP 2 (50 MG/KG)					
12	2.4	5.2	37.2	8.27	1.53
13	2.8	5.8	38.6	9.30	1.65
14	2.3	5.1	38.6	9.44	1.99
16	3.2	7.4	38.6	6.96	2.39
17	2.5	5.6	39.3	9.64	1.83
GROUP 3 (150 MG/KG)					
21	2.6	7.3	40.0	6.23	1.76
22	2.4	5.6	38.6	7.49	2.19
23	2.6	7.0	35.8	9.27	2.23
24	2.2	4.7	36.5	8.39	2.02
25	3.1	5.2	36.5	10.37	2.00

CLINICAL BIOCHEMISTRY
MALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 4 (500 MG/KG)					
31	2.8	6.7	38.6	8.19	2.24
32	2.6	6.9	42.1	9.92	2.69
34	2.8	7.1	38.6	7.63	2.59
35	3.2	6.5	36.5	8.85	2.46
36	2.5	7.5	39.3	10.43	2.48

MALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
1	141.4	4.11	103	2.80	2.34
2	143.1	3.98	103	2.74	2.44
4	142.5	4.39	104	2.67	2.54
6	142.9	4.19	104	2.79	2.52
7	142.3	4.62	103	2.74	2.86
GROUP 2 (50 MG/KG)					
12	144.2	3.78	105	2.67	2.06
13	142.6	3.72	104	2.67	2.09
14	142.9	3.52	103	2.67	2.03
16	142.2	4.02	102	2.83	2.19
17	141.2	3.82	102	2.65	2.64
GROUP 3 (150 MG/KG)					
21	142.0	4.19	103	2.87	2.55
22	141.2	4.03	103	2.78	2.44
23	141.8	4.07	104	2.86	2.26
24	142.3	3.98	104	2.72	2.07
25	140.4	3.98	102	2.82	2.33
GROUP 4 (500 MG/KG)					
31	141.9	3.80	102	2.93	2.46
32	141.4	3.98	102	2.97	2.57
34	141.8	4.02	102	2.81	2.93
35	140.9	4.26	103	2.91	2.67
36	142.5	4.07	104	3.00	2.83

FEMALES
END OF TREATMENT

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 1 (CONTROL)					
42	65.8	87.6	100	61.1	30.1
44	52.8	71.7	83	64.1	31.2
45	62.3	72.8	71	66.1	31.4
47	53.3	68.7	55	62.1	30.5
48	56.2	75.0	82	60.6	30.0

CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	ALAT U/l	ASAT U/l	ALP U/l	Total protein g/l	Albumin g/l
GROUP 2 (50 MG/KG)					
52	53.8	75.6	84	69.1	32.8
53	65.1	95.1	73	62.4	30.3
54	76.4	62.8	126	62.0	30.2
58	45.5	73.3	96	63.2	31.4
59	48.7	64.5	77	65.5	31.9
GROUP 3 (150 MG/KG)					
62	52.8	67.5	165	61.6	30.6
63	47.7	83.5	68	65.6	32.6
64	51.1	70.9	42	64.4	32.7
66	45.6	72.1	59	65.1	32.4
70	55.9	64.4	95	64.9	32.8
GROUP 4 (500 MG/KG)					
71	64.7	89.9	66	63.5	32.4
72	53.0	94.4	61	60.4	31.5
74	70.5	107.5	90	60.6	30.7
78	53.4	81.0	46	61.7	32.0
80	83.5	107.3	88	61.4	31.7

FEMALES
END OF TREATMENT

ANIMAL	Total bilirubin umol/l	Urea mmol/l	Creatinine umol/l	Glucose mmol/l	Cholesterol mmol/l
GROUP 1 (CONTROL)					
42	2.5	7.4	42.7	8.04	1.49
44	2.6	7.4	39.3	6.73	1.37
45	2.6	8.4	41.9	5.94	1.57
47	2.3	7.1	45.3	8.48	1.63
48	2.8	7.1	45.3	8.51	1.70
GROUP 2 (50 MG/KG)					
52	2.5	6.0	38.9	6.15	1.09
53	1.8	7.8	46.4	6.31	2.13
54	2.3	8.4	43.3	6.13	1.67
58	2.3	6.7	37.1	8.06	1.50
59	2.7	7.7	45.9	8.53	1.39
GROUP 3 (150 MG/KG)					
62	2.6	7.9	43.8	7.72	1.69
63	2.7	6.9	46.1	6.70	0.91
64	2.7	6.1	45.1	8.81	1.70
66	3.2	4.2	41.3	8.28	1.35
70	3.7	7.4	43.3	5.49	1.45
GROUP 4 (500 MG/KG)					
71	3.1	6.1	42.7	7.15	1.68
72	4.1	7.0	40.6	7.77	1.14
74	2.1	7.5	43.4	6.65	0.91
78	2.6	7.1	39.3	6.73	1.19
80	3.2	7.2	43.9	6.88	1.43

CLINICAL BIOCHEMISTRY
FEMALES
END OF TREATMENT

ANIMAL	Sodium mmol/l	Potassium mmol/l	Chloride mmol/l	Calcium mmol/l	Inorg.Phos mmol/l
GROUP 1 (CONTROL)					
42	138.4	3.81	100	2.50	1.80
44	136.1	4.17	99	2.61	1.76
45	137.7	3.43	101	2.57	2.01
47	137.6	3.80	98	2.65	1.65
48	139.2	3.70	100	2.56	2.14
GROUP 2 (50 MG/KG)					
52	137.0	4.07	99	2.64	1.70
53	140.3	2.52	98	2.51	2.20
54	139.2	3.95	101	2.59	2.33
58	136.8	3.70	98	2.56	1.89
59	138.2	4.05	100	2.58	1.89
GROUP 3 (150 MG/KG)					
62	137.3	3.55	98	2.55	2.37
63	137.3	3.00	97	2.60	1.82
64	139.0	2.80	96	2.60	1.87
66	135.5	3.48	97	2.65	1.66
70	138.8	3.73	101	2.76	2.10
GROUP 4 (500 MG/KG)					
71	136.3	3.89	99	2.81	2.58
72	136.6	3.99	100	2.73	2.05
74	136.4	3.93	101	2.63	2.17
78	139.5	3.70	101	2.82	1.82
80	137.2	3.75	101	2.67	1.91

MACROSCOPIC FINDINGS
MALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
1		No findings noted	Scheduled sacrifice, 08Feb2007
2		No findings noted	Scheduled sacrifice, 08Feb2007
3		No findings noted	Scheduled sacrifice, 08Feb2007
4		No findings noted	Scheduled sacrifice, 08Feb2007
5	Kidneys	Right side: pelvic dilation.	Scheduled sacrifice, 08Feb2007
6	Bone	Tail apex: bent.	Scheduled sacrifice, 08Feb2007
7		No findings noted	Scheduled sacrifice, 08Feb2007
8		No findings noted	Scheduled sacrifice, 08Feb2007
9		No findings noted	Scheduled sacrifice, 08Feb2007
10		No findings noted	Scheduled sacrifice, 08Feb2007
GROUP 2 (50 MG/KG)			
11		No findings noted	Scheduled sacrifice, 08Feb2007
12		No findings noted	Scheduled sacrifice, 08Feb2007
13		No findings noted	Scheduled sacrifice, 08Feb2007
14		No findings noted	Scheduled sacrifice, 08Feb2007
15	Bone	Tail apex: bent.	Scheduled sacrifice, 08Feb2007
16		No findings noted	Scheduled sacrifice, 08Feb2007
17		No findings noted	Scheduled sacrifice, 08Feb2007
18		No findings noted	Scheduled sacrifice, 08Feb2007
19		No findings noted	Scheduled sacrifice, 08Feb2007
20	Seminal vesicles	Right side: reduced in size.	Scheduled sacrifice, 08Feb2007
GROUP 3 (150 MG/KG)			
21		No findings noted	Scheduled sacrifice, 08Feb2007
22		No findings noted	Scheduled sacrifice, 08Feb2007
23		No findings noted	Scheduled sacrifice, 08Feb2007
24		No findings noted	Scheduled sacrifice, 08Feb2007
25		No findings noted	Scheduled sacrifice, 08Feb2007
26		No findings noted	Scheduled sacrifice, 08Feb2007
27		No findings noted	Scheduled sacrifice, 08Feb2007
28		No findings noted	Scheduled sacrifice, 08Feb2007
29		No findings noted	Scheduled sacrifice, 08Feb2007
30	Seminal vesicles	Left side: reduced in size.	Scheduled sacrifice, 08Feb2007
GROUP 4 (500 MG/KG)			
31	Liver	Discolouration, pale.	Scheduled sacrifice, 08Feb2007
32		No findings noted	Scheduled sacrifice, 08Feb2007
33	Liver	Discolouration, pale.	Scheduled sacrifice, 08Feb2007
34		No findings noted	Scheduled sacrifice, 08Feb2007
35	Liver	Discolouration, pale.	Scheduled sacrifice, 08Feb2007
36	Liver	Discolouration, pale.	Scheduled sacrifice, 08Feb2007
37		No findings noted	Scheduled sacrifice, 08Feb2007
38		No findings noted	Scheduled sacrifice, 08Feb2007
39		No findings noted	Scheduled sacrifice, 08Feb2007
40	Liver	Discolouration, pale.	Scheduled sacrifice, 08Feb2007

FEMALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
41		No findings noted	Scheduled sacrifice, 22Feb2007
42	Mandibular l.node	Right side: discolouration, dark red.	Scheduled sacrifice, 21Feb2007
43		No findings noted	Scheduled sacrifice, 19Feb2007
44		No findings noted	Scheduled sacrifice, 20Feb2007
45		No findings noted	Scheduled sacrifice, 20Feb2007
46		No findings noted	Scheduled sacrifice, 19Feb2007
47	Mandibular l.node	Both sides: discolouration, dark red.	Scheduled sacrifice, 20Feb2007

MACROSCOPIC FINDINGS
FEMALES
ALL NECROPSIES

ANIMAL	ORGAN	FINDING	DAY OF DEATH
GROUP 1 (CONTROL)			
48		No findings noted	Scheduled sacrifice, 20Feb2007
49		No findings noted	Scheduled sacrifice, 21Feb2007
50		No findings noted	Scheduled sacrifice, 21Feb2007
GROUP 2 (50 MG/KG)			
51	Uterus	Enlarged. Contains fluid.	Scheduled sacrifice, 21Feb2007
	Cervix	Enlarged.	
52		No findings noted	Scheduled sacrifice, 22Feb2007
53	Adrenal glands	Both sides: enlarged.	Scheduled sacrifice, 19Feb2007
54		No findings noted	Scheduled sacrifice, 20Feb2007
55		No findings noted	Scheduled sacrifice, 21Feb2007
56		No findings noted	Scheduled sacrifice, 22Feb2007
57		No findings noted	Scheduled sacrifice, 22Feb2007
58		No findings noted	Scheduled sacrifice, 19Feb2007
59	Skin	Hindleg, right side: alopecia.	Scheduled sacrifice, 20Feb2007
60	Stomach	Contents: reddish.	Other, 15Feb2007
GROUP 3 (150 MG/KG)			
61		No findings noted	Scheduled sacrifice, 22Feb2007
62		No findings noted	Scheduled sacrifice, 19Feb2007
63		No findings noted	Scheduled sacrifice, 21Feb2007
64		No findings noted	Scheduled sacrifice, 19Feb2007
65		No findings noted	Scheduled sacrifice, 19Feb2007
66	Liver	Right lateral lobe: diaphragmatic Hernia.	Scheduled sacrifice, 21Feb2007
67		No findings noted	Scheduled sacrifice, 21Feb2007
68		No findings noted	Scheduled sacrifice, 21Feb2007
69		No findings noted	Scheduled sacrifice, 19Feb2007
70		No findings noted	Scheduled sacrifice, 20Feb2007
GROUP 4 (500 MG/KG)			
71	Mandibular l.node	Right side: discolouration, dark red.	Scheduled sacrifice, 21Feb2007
72	Lungs	Focus/foci, many, gray-white.	Scheduled sacrifice, 20Feb2007
73		No findings noted	Scheduled sacrifice, 21Feb2007
74	Lungs	Focus/foci, many, gray-white.	Scheduled sacrifice, 21Feb2007
75		No findings noted	Scheduled sacrifice, 21Feb2007
76		No findings noted	Scheduled sacrifice, 21Feb2007
77		No findings noted	Scheduled sacrifice, 21Feb2007
78	Lungs	Focus/foci, many, gray-white.	Scheduled sacrifice, 20Feb2007
79		No findings noted	Other, 17Feb2007
80	Lungs	Focus/foci, many, gray-white.	Scheduled sacrifice, 20Feb2007

ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
1	451	2.03	1.348	12.08	0.619
2	413	2.02	1.319	10.65	0.324
3	444	---	---	---	---
4	410	1.89	1.149	9.95	0.417
5	421	---	---	---	---
6	437	2.13	1.240	11.73	0.532
7	451	2.14	1.259	12.94	0.445
8	397	---	---	---	---
9	380	---	---	---	---
10	437	---	---	---	---
GROUP 2 (50 MG/KG)					
11	453	---	---	---	---
12	407	2.21	1.273	10.47	0.334
13	410	2.03	1.285	10.75	0.338
14	420	2.13	1.257	10.65	0.369
15	381	---	---	---	---
16	395	2.20	1.405	10.41	0.450
17	410	2.11	1.391	9.82	0.269
18	408	---	---	---	---
19	422	---	---	---	---
20	458	---	---	---	---
GROUP 3 (150 MG/KG)					
21	411	2.25	1.389	11.26	0.405
22	459	2.11	1.490	11.30	0.556
23	375	1.95	1.212	9.74	0.236
24	386	2.11	1.203	9.23	0.311
25	464	2.01	1.447	13.12	0.386
26	400	---	---	---	---
27	455	---	---	---	---
28	425	---	---	---	---
29	396	---	---	---	---
30	388	---	---	---	---
GROUP 4 (500 MG/KG)					
31	412	2.15	1.405	12.49	0.242
32	410	2.11	1.380	11.50	0.347
33	410	---	---	---	---
34	408	2.07	1.453	12.90	0.284
35	381	2.06	1.446	12.98	0.305
36	384	2.08	1.398	12.44	0.248
37	391	---	---	---	---
38	411	---	---	---	---
39	393	---	---	---	---
40	428	---	---	---	---

ORGAN WEIGHTS (GRAM)
MALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)	TESTES (GRAM)	EPIDIDYMIDES (GRAM)
GROUP 1 (CONTROL)					
1	3.00	0.068	1.052	3.48	1.054
2	3.29	0.070	1.096	4.51	1.448
3	---	---	---	4.10	1.357
4	2.82	0.068	0.781	3.83	1.167
5	---	---	---	4.34	1.224
6	3.17	0.046	1.219	3.92	1.181
7	3.50	0.085	1.250	4.01	1.229
8	---	---	---	4.10	1.142
9	---	---	---	3.86	1.344
10	---	---	---	4.25	1.353
GROUP 2 (50 MG/KG)					
11	---	---	---	3.66	1.351
12	3.20	0.067	0.937	4.14	1.187
13	2.93	0.073	0.938	3.79	1.150
14	2.96	0.087	0.841	3.70	1.262
15	---	---	---	3.62	1.209
16	3.00	0.058	1.086	3.60	1.290
17	3.54	0.066	0.816	3.01	1.024
18	---	---	---	3.72	1.284
19	---	---	---	3.92	1.313
20	---	---	---	3.78	1.199
GROUP 3 (150 MG/KG)					
21	2.82	0.076	1.072	3.58	1.182
22	3.63	0.064	1.084	4.18	1.248
23	2.96	0.059	0.846	3.64	1.124
24	2.88	0.079	0.889	3.49	1.163
25	3.19	0.074	1.223	4.30	1.242
26	---	---	---	3.86	1.074
27	---	---	---	3.69	1.157
28	---	---	---	3.79	1.176
29	---	---	---	4.21	1.166
30	---	---	---	3.70	1.158
GROUP 4 (500 MG/KG)					
31	3.19	0.085	0.866	3.74	1.013
32	3.13	0.082	1.013	3.99	0.909
33	---	---	---	3.97	1.058
34	3.48	0.085	0.913	4.22	1.032
35	3.09	0.076	0.835	3.58	1.021
36	2.88	0.062	0.820	3.83	0.995
37	---	---	---	3.87	0.886
38	---	---	---	4.57	1.148
39	---	---	---	3.84	1.172
40	---	---	---	4.35	1.124

ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
1	451	0.45	0.299	2.68	0.137
2	413	0.49	0.319	2.58	0.078
3	444	---	---	---	---
4	410	0.46	0.280	2.43	0.102
5	421	---	---	---	---
6	437	0.49	0.284	2.68	0.122
7	451	0.47	0.279	2.87	0.099
8	397	---	---	---	---
9	380	---	---	---	---
10	437	---	---	---	---
GROUP 2 (50 MG/KG)					
11	453	---	---	---	---
12	407	0.54	0.313	2.57	0.082
13	410	0.49	0.313	2.62	0.082
14	420	0.51	0.299	2.53	0.088
15	381	---	---	---	---
16	395	0.56	0.356	2.63	0.114
17	410	0.51	0.339	2.39	0.066
18	408	---	---	---	---
19	422	---	---	---	---
20	458	---	---	---	---
GROUP 3 (150 MG/KG)					
21	411	0.55	0.338	2.74	0.099
22	459	0.46	0.325	2.46	0.121
23	375	0.52	0.323	2.60	0.063
24	386	0.55	0.312	2.39	0.081
25	464	0.43	0.312	2.83	0.083
26	400	---	---	---	---
27	455	---	---	---	---
28	425	---	---	---	---
29	396	---	---	---	---
30	388	---	---	---	---
GROUP 4 (500 MG/KG)					
31	412	0.52	0.341	3.03	0.059
32	410	0.51	0.337	2.80	0.085
33	410	---	---	---	---
34	408	0.51	0.356	3.16	0.070
35	381	0.54	0.380	3.41	0.080
36	384	0.54	0.364	3.24	0.065
37	391	---	---	---	---
38	411	---	---	---	---
39	393	---	---	---	---
40	428	---	---	---	---

ORGAN/BODY WEIGHT RATIOS (%)
MALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIDES (%)
GROUP 1 (CONTROL)					
1	0.66	0.015	0.233	0.77	0.234
2	0.80	0.017	0.265	1.09	0.351
3	---	---	---	0.92	0.306
4	0.69	0.017	0.190	0.93	0.285
5	---	---	---	1.03	0.291
6	0.72	0.011	0.279	0.90	0.270
7	0.78	0.019	0.277	0.89	0.273
8	---	---	---	1.03	0.288
9	---	---	---	1.02	0.354
10	---	---	---	0.97	0.310
GROUP 2 (50 MG/KG)					
11	---	---	---	0.81	0.298
12	0.79	0.016	0.230	1.02	0.292
13	0.71	0.018	0.229	0.93	0.280
14	0.70	0.021	0.200	0.88	0.300
15	---	---	---	0.95	0.317
16	0.76	0.015	0.275	0.91	0.327
17	0.86	0.016	0.199	0.73	0.250
18	---	---	---	0.91	0.315
19	---	---	---	0.93	0.311
20	---	---	---	0.83	0.262
GROUP 3 (150 MG/KG)					
21	0.69	0.018	0.261	0.87	0.288
22	0.79	0.014	0.236	0.91	0.272
23	0.79	0.016	0.226	0.97	0.300
24	0.75	0.020	0.230	0.90	0.301
25	0.69	0.016	0.264	0.93	0.268
26	---	---	---	0.97	0.269
27	---	---	---	0.81	0.254
28	---	---	---	0.89	0.277
29	---	---	---	1.06	0.294
30	---	---	---	0.95	0.298
GROUP 4 (500 MG/KG)					
31	0.77	0.021	0.210	0.91	0.246
32	0.76	0.020	0.247	0.97	0.222
33	---	---	---	0.97	0.258
34	0.85	0.021	0.224	1.04	0.253
35	0.81	0.020	0.219	0.94	0.268
36	0.75	0.016	0.214	1.00	0.259
37	---	---	---	0.99	0.227
38	---	---	---	1.11	0.279
39	---	---	---	0.98	0.298
40	---	---	---	1.02	0.263

ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (GRAM)	HEART (GRAM)	LIVER (GRAM)	THYMUS (GRAM)
GROUP 1 (CONTROL)					
41	---	---	---	---	---
42	247	2.00	0.975	9.46	0.183
43	---	---	---	---	---
44	262	1.88	0.902	9.21	0.253
45	271	1.85	0.925	8.99	0.190
46	---	---	---	---	---
47	276	1.93	0.906	8.74	0.298
48	285	1.89	1.043	9.71	0.216
49	---	---	---	---	---
50	---	---	---	---	---
GROUP 2 (50 MG/KG)					
51	---	---	---	---	---
52	280	2.01	1.067	9.94	0.229
53	299	1.94	1.029	10.63	0.203
54	281	1.88	0.904	10.02	0.192
55	---	---	---	---	---
56	---	---	---	---	---
57	---	---	---	---	---
58	269	1.84	1.025	9.85	0.179
59	299	1.88	1.001	10.70	0.327
60	---	---	---	---	---
GROUP 3 (150 MG/KG)					
61	---	---	---	---	---
62	292	1.99	0.981	9.60	0.228
63	271	1.85	0.955	9.31	0.196
64	282	1.85	1.086	11.19	0.185
65	---	---	---	---	---
66	270	1.80	1.046	9.60	0.195
67	---	---	---	---	---
68	---	---	---	---	---
69	---	---	---	---	---
70	302	1.95	0.995	9.54	0.199
GROUP 4 (500 MG/KG)					
71	263	1.86	1.064	9.40	0.177
72	282	1.86	1.037	8.72	0.166
73	---	---	---	---	---
74	291	1.92	1.142	9.58	0.149
75	---	---	---	---	---
76	---	---	---	---	---
77	---	---	---	---	---
78	246	1.80	1.040	8.65	0.116
79	---	---	---	---	---
80	271	1.77	0.961	10.01	0.184

ORGAN WEIGHTS (GRAM)
FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (GRAM)	ADRENALS (GRAM)	SPLEEN (GRAM)
GROUP 1 (CONTROL)			
41	---	---	---
42	2.10	0.094	0.941
43	---	---	---
44	1.95	0.103	0.841
45	1.83	0.100	0.910
46	---	---	---
47	2.21	0.083	0.869
48	1.97	0.087	0.863
49	---	---	---
50	---	---	---
GROUP 2 (50 MG/KG)			
51	---	---	---
52	2.27	0.110	0.847
53	2.41	0.130	0.978
54	2.01	0.102	0.760
55	---	---	---
56	---	---	---
57	---	---	---
58	2.15	0.091	0.802
59	1.93	0.105	0.995
60	---	---	---
GROUP 3 (150 MG/KG)			
61	---	---	---
62	2.40	0.102	0.820
63	2.11	0.111	1.029
64	2.32	0.127	1.122
65	---	---	---
66	2.21	0.115	0.802
67	---	---	---
68	---	---	---
69	---	---	---
70	2.27	0.113	0.577
GROUP 4 (500 MG/KG)			
71	2.38	0.112	0.733
72	2.56	0.109	0.647
73	---	---	---
74	2.53	0.110	0.870
75	---	---	---
76	---	---	---
77	---	---	---
78	2.20	0.127	0.553
79	---	---	---
80	2.18	0.106	0.654

ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)
GROUP 1 (CONTROL)					
41	---	---	---	---	---
42	247	0.81	0.395	3.83	0.074
43	---	---	---	---	---
44	262	0.72	0.344	3.52	0.097
45	271	0.68	0.341	3.32	0.070
46	---	---	---	---	---
47	276	0.70	0.328	3.17	0.108
48	285	0.66	0.366	3.41	0.076
49	---	---	---	---	---
50	---	---	---	---	---
GROUP 2 (50 MG/KG)					
51	---	---	---	---	---
52	280	0.72	0.381	3.55	0.082
53	299	0.65	0.344	3.56	0.068
54	281	0.67	0.322	3.57	0.068
55	---	---	---	---	---
56	---	---	---	---	---
57	---	---	---	---	---
58	269	0.68	0.381	3.66	0.067
59	299	0.63	0.335	3.58	0.109
60	---	---	---	---	---
GROUP 3 (150 MG/KG)					
61	---	---	---	---	---
62	292	0.68	0.336	3.29	0.078
63	271	0.68	0.352	3.44	0.072
64	282	0.66	0.385	3.97	0.066
65	---	---	---	---	---
66	270	0.67	0.387	3.56	0.072
67	---	---	---	---	---
68	---	---	---	---	---
69	---	---	---	---	---
70	302	0.65	0.329	3.16	0.066
GROUP 4 (500 MG/KG)					
71	263	0.71	0.405	3.58	0.067
72	282	0.66	0.368	3.09	0.059
73	---	---	---	---	---
74	291	0.66	0.392	3.29	0.051
75	---	---	---	---	---
76	---	---	---	---	---
77	---	---	---	---	---
78	246	0.73	0.423	3.52	0.047
79	---	---	---	---	---
80	271	0.65	0.355	3.69	0.068

ORGAN/BODY WEIGHT RATIOS (%)
FEMALES
END OF TREATMENT

ANIMAL	KIDNEYS (%)	ADRENALS (%)	SPLEEN (%)
GROUP 1 (CONTROL)			
41	---	---	---
42	0.85	0.038	0.381
43	---	---	---
44	0.74	0.039	0.321
45	0.67	0.037	0.336
46	---	---	---
47	0.80	0.030	0.315
48	0.69	0.031	0.303
49	---	---	---
50	---	---	---
GROUP 2 (50 MG/KG)			
51	---	---	---
52	0.81	0.039	0.303
53	0.80	0.043	0.327
54	0.71	0.036	0.270
55	---	---	---
56	---	---	---
57	---	---	---
58	0.80	0.034	0.298
59	0.64	0.035	0.333
60	---	---	---
GROUP 3 (150 MG/KG)			
61	---	---	---
62	0.82	0.035	0.281
63	0.78	0.041	0.380
64	0.82	0.045	0.398
65	---	---	---
66	0.82	0.043	0.297
67	---	---	---
68	---	---	---
69	---	---	---
70	0.75	0.037	0.191
GROUP 4 (500 MG/KG)			
71	0.90	0.043	0.279
72	0.91	0.039	0.229
73	---	---	---
74	0.87	0.038	0.299
75	---	---	---
76	---	---	---
77	---	---	---
78	0.89	0.052	0.225
79	---	---	---
80	0.80	0.039	0.241

BREEDING DATA PER LITTER
F0-GENERATION - LACTATION

LITTER	DURATION OF GESTATION	-- FIRST LITTER CHECK -- DEAD PUPS M	F	LIVING PUPS M	F	TOT.	P.NATAL LOSS M	F
GROUP 1 (CONTROL)								
41	22	0	0	12	6	18	0	0
42	21	1	0	10	9	19	0	0
43	21	1	0	3	11	14	0	0
44	21	0	0	6	10	16	0	0
45	20	0	0	9	6	15	0	0
46	22	0	0	8	6	14	0	0
47	22	0	0	5	10	15	0	0
48	20	0	0	6	10	16	0	0
49	22	0	0	6	11	17	0	0
TOTAL		2	0	65	79	144	0	0
N	9	9	9	9	9	9	9	9
MEAN	21.2	0.2	0.0	7.2	8.8	16.0	0.0	0.0
ST.DEV.	0.8	0.4	0.0	2.8	2.2	1.7	0.0	0.0

BREEDING DATA PER LITTER
F0-GENERATION - LACTATION

LITTER	DURATION OF GESTATION	-- FIRST LITTER CHECK -- DEAD PUPS M	F	LIVING PUPS M	F	TOT.	P.NATAL LOSS M	F
GROUP 2 (50 MG/KG)								
52	22	0	0	8	8	16	0	1
53	21	1	0	12	6	18	0	0
54	21	0	0	11	7	18	0	0
56	22	0	0	4	3	7	0	0
57	22	0	0	2	13	15	0	1
58	21	0	0	7	10	17	0	0
59	21	0	0	6	10	16	0	0
60	22	0	0	1	12	13	1	12
TOTAL		1	0	51	69	120	1	14
N	8	8	8	8	8	8	8	8
MEAN	21.5	0.1	0.0	6.4	8.6	15.0	0.1	1.8
ST.DEV.	0.5	0.4	0.0	4.0	3.3	3.6	0.4	4.2

BREEDING DATA PER LITTER
F0-GENERATION - LACTATION

LITTER	DURATION OF GESTATION	-- FIRST LITTER CHECK -- DEAD PUPS M	F	LIVING PUPS M	F	TOT.	P.NATAL LOSS M	F
GROUP 3 (150 MG/KG)								
61	22	0	0	8	9	17	0	0
62	21	0	0	8	6	14	1	0
63	22	0	0	11	9	20	0	2
64	21	0	0	4	14	18	0	0
65	21	0	0	6	7	13	0	0
66	20	0	0	8	8	16	0	0
67	21	0	0	7	10	17	0	1
68	22	0	0	11	6	17	3	1
69	21	0	0	7	11	18	2	0
70	21	2	1	11	6	17	0	0
TOTAL		2	1	81	86	167	6	4
N	10	10	10	10	10	10	10	10
MEAN	21.2	0.2	0.1	8.1	8.6	16.7	0.6	0.4
ST.DEV.	0.6	0.6	0.3	2.3	2.6	2.0	1.1	0.7

BREEDING DATA PER LITTER
F0-GENERATION - LACTATION

LITTER	DURATION OF GESTATION	-- FIRST LITTER CHECK -- DEAD PUPS M	F	LIVING PUPS M	F	TOT.	P.NATAL LOSS M	F
GROUP 4 (500 MG/KG)								
71	22	0	0	2	2	4	0	0
72	22	0	0	5	2	7	0	0
74	22	0	0	5	4	9	0	0
76	22	0	0	2	6	8	0	0
78	22	0	0	6	5	11	4	4
79	21	3	0	0	2	2	0	2
80	22	0	0	3	4	7	0	0
TOTAL		3	0	23	25	48	4	6
N	7	7	7	7	7	7	7	7
MEAN	21.9	0.4	0.0	3.3	3.6	6.9	0.6	0.9
ST.DEV.	0.4	1.1	0.0	2.1	1.6	3.0	1.5	1.6

MEAN BODY WEIGHTS OF PUPS PER LITTER (GRAM)
F0-GENERATION - LACTATION

LITTER	SEX	DAY 1	DAY 4
GROUP 1 (CONTROL)			
41	M	6.4	9.3
	F	5.9	7.8
	M+F	6.2	8.8
42	M	5.9	8.4
	F	5.7	7.7
	M+F	5.8	8.1
43	M	6.6	9.7
	F	6.4	9.5
	M+F	6.4	9.6
44	M	6.0	8.5
	F	5.5	7.7
	M+F	5.7	8.0
45	M	6.6	8.9
	F	6.0	8.4
	M+F	6.3	8.7
46	M	7.3	11.5
	F	7.3	11.2
	M+F	7.3	11.4
47	M	7.4	10.8
	F	6.9	10.4
	M+F	7.1	10.6
48	M	6.4	8.8
	F	5.9	8.1
	M+F	6.1	8.3
49	M	6.6	9.8
	F	6.3	9.2
	M+F	6.4	9.4
GROUP 2 (50 MG/KG)			
52	M	6.6	10.2
	F	6.4	9.6
	M+F	6.5	9.9
53	M	6.5	9.4
	F	6.1	8.5
	M+F	6.4	9.1
54	M	6.3	8.8
	F	5.8	7.7
	M+F	6.1	8.4
56	M	7.8	13.0
	F	7.8	13.0
	M+F	7.8	13.0
57	M	6.3	10.3
	F	6.1	9.8
	M+F	6.2	9.8
58	M	6.4	9.1
	F	6.0	8.6
	M+F	6.2	8.8
59	M	6.7	10.2
	F	6.3	9.6
	M+F	6.5	9.8
60	M	7.4	--
	F	7.3	--
	M+F	7.3	--

MEAN BODY WEIGHTS OF PUPS PER LITTER (GRAM)
F0-GENERATION - LACTATION

LITTER	SEX	DAY 1	DAY 4
GROUP 3 (150 MG/KG)			
61	M	6.7	9.1
	F	5.8	7.7
	M+F	6.2	8.3
62	M	6.4	9.1
	F	6.0	8.4
	M+F	6.2	8.8
63	M	6.3	9.2
	F	5.8	8.4
	M+F	6.1	8.9
64	M	6.3	9.1
	F	6.0	8.2
	M+F	6.0	8.4
65	M	6.1	9.6
	F	6.1	9.5
	M+F	6.1	9.6
66	M	6.4	8.4
	F	5.8	7.4
	M+F	6.1	7.9
67	M	6.3	9.1
	F	5.9	8.4
	M+F	6.1	8.7
68	M	6.9	10.9
	F	6.2	9.8
	M+F	6.7	10.5
69	M	5.9	8.4
	F	5.3	7.7
	M+F	5.6	7.9
70	M	6.1	8.1
	F	5.7	7.5
	M+F	5.9	7.9
GROUP 4 (500 MG/KG)			
71	M	7.6	11.1
	F	6.6	9.9
	M+F	7.1	10.5
72	M	6.2	9.2
	F	6.8	10.3
	M+F	6.3	9.5
74	M	6.3	9.5
	F	6.7	10.2
	M+F	6.5	9.8
76	M	7.6	11.2
	F	6.6	9.8
	M+F	6.8	10.2
78	M	5.6	8.0
	F	5.4	7.3
	M+F	5.5	7.8
79	M	--	--
	F	5.3	--
	M+F	5.3	--
80	M	7.0	10.8
	F	6.7	10.3
	M+F	6.8	10.5

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 1 (CONTROL)				
41	1	M	6.8	10.3
	2	M	5.6	8.2
	3	M	5.9	8.8
	4	M	6.7	9.2
	5	M	7.0	10.0
	6	M	6.4	10.1
	7	M	6.6	9.8
	8	M	6.1	8.6
	9	M	6.4	8.7
	10	M	6.1	9.2
	11	M	6.5	9.4
	12	M	6.2	9.1
	13	F	6.1	8.5
	14	F	5.5	7.3
	15	F	5.6	7.6
	16	F	6.4	9.5
	17	F	5.2	5.8
	18	F	6.4	8.2
42	1	M	5.8	8.8
	2	M	6.0	8.7
	3	M	6.1	8.9
	4	M	6.1	8.7
	5	M	6.3	9.1
	6	M	5.1	6.5
	7	M	5.6	8.5
	8	M	5.5	8.2
	9	M	6.7	8.9
	10	M	--	--
	11	F	5.7	7.9
	12	F	5.8	7.9
	13	F	5.5	7.4
	14	M	6.2	8.2
	15	F	5.5	7.3
	16	F	5.8	8.0
	17	F	5.2	7.7
	18	F	5.2	6.9
	19	F	6.0	8.5
	20	F	6.2	7.9
43	1	M	6.4	10.0
	2	M	6.7	9.0
	3	M	6.5	9.9
	4	M	--	--
	5	F	6.3	9.4
	6	F	6.8	10.0
	7	F	6.4	9.5
	8	F	6.4	10.2
	9	F	6.6	10.2
	10	F	5.9	9.1
	11	F	6.1	8.7
	12	F	6.6	9.6
	13	F	6.3	9.9
	14	F	6.0	8.8
	15	F	6.6	9.4
44	1	M	5.7	8.3
	2	M	6.5	9.7
	3	M	5.7	7.4
	4	M	6.1	8.6
	5	M	5.7	8.1
	6	M	6.3	8.9
	7	F	6.0	8.5
	8	F	5.9	8.8
	9	F	5.4	7.4
	10	F	5.4	8.3

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 1 (CONTROL)				
	11	F	5.2	6.9
	12	F	5.9	8.6
	13	F	5.0	6.2
	14	F	5.0	6.9
	15	F	5.7	8.1
	16	F	5.1	7.0
45	1	M	5.9	7.8
	2	M	6.9	9.6
	3	M	6.6	8.1
	4	M	6.9	9.3
	5	M	6.8	8.8
	6	M	6.9	9.7
	7	M	6.3	8.7
	8	M	6.3	9.0
	9	M	6.5	9.4
	10	F	6.0	9.1
	11	F	6.0	8.7
	12	F	6.5	9.1
	13	F	5.5	7.6
	14	F	5.7	7.8
	15	F	6.2	8.3
46	1	M	7.9	12.4
	2	M	7.0	11.6
	3	M	7.2	10.8
	4	M	6.9	11.2
	5	M	7.0	10.8
	6	M	7.6	11.9
	7	M	7.1	11.2
	8	M	7.3	11.9
	9	F	7.3	11.0
	10	F	7.3	11.3
	11	F	7.2	11.3
	12	F	7.1	10.5
	13	F	7.4	11.7
	14	F	7.6	11.4
47	1	M	7.5	11.4
	2	M	7.1	10.0
	3	M	7.3	10.3
	4	M	7.1	10.8
	5	M	8.0	11.7
	6	F	7.1	11.3
	7	F	6.5	10.1
	8	F	7.0	10.7
	9	F	6.9	10.9
	10	F	7.2	10.3
	11	F	6.7	10.5
	12	F	6.5	10.1
	13	F	7.4	10.6
	14	F	6.6	9.6
	15	F	7.0	10.3
48	1	M	7.0	9.9
	2	M	6.7	9.2
	3	M	6.1	8.4
	4	M	5.8	7.8
	5	F	6.5	8.7
	6	F	5.4	7.5
	7	M	6.9	9.6
	8	M	6.0	7.9
	9	F	6.0	8.8
	10	F	6.0	8.1
	11	F	6.2	8.3
	12	F	6.4	9.0
	13	F	6.4	8.8

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 1 (CONTROL)				
	14	F	4.8	5.8
	15	F	5.6	7.4
	16	F	5.9	8.3
49	1	M	7.0	11.2
	2	M	5.8	8.2
	3	M	7.2	10.0
	4	M	7.4	11.3
	5	M	6.0	9.3
	6	M	6.2	9.0
	7	F	6.4	9.9
	8	F	5.8	8.3
	9	F	5.6	8.3
	10	F	6.6	9.8
	11	F	5.8	8.5
	12	F	6.2	9.5
	13	F	6.7	9.3
	14	F	6.2	8.3
	15	F	6.7	8.5
	16	F	6.8	10.3
	17	F	6.7	10.3
GROUP 2 (50 MG/KG)				
52	1	M	6.8	11.6
	2	M	6.4	9.5
	3	M	6.1	9.3
	4	M	6.7	11.1
	5	M	6.8	10.2
	6	M	6.5	9.8
	7	M	6.7	9.8
	8	M	6.6	10.2
	9	F	6.6	8.5
	10	F	6.0	9.9
	11	F	6.1	9.6
	12	F	6.2	9.3
	13	F	6.6	--
	14	F	6.4	9.5
	15	F	6.7	10.1
	16	F	6.3	10.2
53	1	M	6.3	9.2
	2	M	6.8	9.8
	3	M	6.8	9.2
	4	M	6.1	9.2
	5	M	6.4	9.1
	6	M	6.5	9.6
	7	M	6.6	9.5
	8	M	7.1	9.9
	9	M	6.5	9.3
	10	M	6.1	9.0
	11	M	6.3	8.9
	12	M	6.5	9.6
	13	M	--	--
	14	F	6.1	8.6
	15	F	5.8	8.2
	16	F	6.1	8.3
	17	F	6.4	9.2
	18	F	5.9	8.2
	19	F	6.1	8.2

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 2 (50 MG/KG)				
54	1	M	6.4	8.9
	2	M	6.5	9.2
	3	M	6.1	8.6
	4	M	6.0	8.1
	5	M	6.5	9.3
	6	M	6.3	8.4
	7	M	6.1	8.5
	8	M	6.6	10.1
	9	M	6.4	9.2
	10	M	6.1	8.8
	11	F	6.2	8.3
	12	F	6.0	8.9
	13	F	5.7	7.7
	14	M	5.9	8.0
	15	F	5.5	7.1
	16	F	5.8	6.8
	17	F	5.8	7.5
	18	F	5.6	8.0
56	1	M	8.1	13.5
	2	M	7.6	12.2
	3	M	7.6	13.3
	4	M	7.9	13.2
	5	F	7.7	13.1
	6	F	7.9	13.3
	7	F	7.7	12.5
57	1	M	6.8	10.9
	2	M	5.8	9.8
	3	F	5.9	9.6
	4	F	5.8	8.4
	5	F	6.5	10.3
	6	F	5.8	9.4
	7	F	6.2	9.8
	8	F	6.7	9.9
	9	F	5.5	--
	10	F	6.8	11.5
	11	F	5.1	7.5
	12	F	6.3	10.0
	13	F	5.9	9.2
	14	F	7.0	11.6
	15	F	6.3	9.9
58	1	M	6.1	9.2
	2	F	5.9	8.4
	3	M	6.6	9.5
	4	M	6.2	7.8
	5	M	6.5	9.3
	6	M	6.0	8.9
	7	M	6.6	9.6
	8	M	6.5	9.5
	9	F	5.8	8.8
	10	F	6.0	9.1
	11	F	6.5	9.2
	12	F	6.2	8.8
	13	F	6.3	9.6
	14	F	5.8	7.2
	15	F	6.3	8.9
	16	F	5.9	8.3
	17	F	5.8	7.9

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 2 (50 MG/KG)				
59	1	M	6.2	9.8
	2	M	7.1	11.4
	3	M	6.3	8.9
	4	M	6.7	10.5
	5	F	6.0	8.9
	6	M	6.7	10.0
	7	M	7.2	10.9
	8	F	6.2	9.0
	9	F	6.0	9.4
	10	F	6.6	10.1
	11	F	5.9	9.2
	12	F	6.8	9.9
	13	F	7.0	10.7
	14	F	6.5	9.8
	15	F	6.0	9.7
	16	F	6.2	9.4
60	1	M	7.4	
	2	F	7.6	
	3	F	6.8	
	4	F	7.7	
	5	F	7.8	
	6	F	7.4	
	7	F	7.2	
	8	F	6.8	
	9	F	7.5	
	10	F	6.9	
	11	F	7.7	
	12	F	7.0	
	13	F	7.5	
GROUP 3 (150 MG/KG)				
61	1	M	6.7	8.9
	2	M	6.4	8.8
	3	M	6.8	9.5
	4	M	7.1	9.2
	5	M	6.6	8.6
	6	M	6.6	9.2
	7	M	6.7	9.5
	8	M	6.5	8.8
	9	F	5.9	8.1
	10	F	6.2	7.9
	11	F	6.4	8.7
	12	F	5.6	7.7
	13	F	5.7	7.7
	14	F	5.8	8.0
	15	F	5.7	7.4
	16	F	5.4	6.7
	17	F	5.3	6.7
62	1	M	5.8	8.5
	2	M	6.7	8.5
	3	M	6.4	9.4
	4	M	6.4	9.1
	5	M	6.2	8.9
	6	M	6.1	9.4
	7	M	6.7	9.3
	8	M	6.7	9.6
	9	F	5.9	8.9
	10	F	5.9	8.9
	11	F	6.2	9.4
	12	F	5.9	8.0
	13	F	6.0	7.9
	14	F	6.0	7.2

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 3 (150 MG/KG)				
63	1	M	7.2	10.2
	2	M	6.2	9.0
	3	M	6.3	9.0
	4	M	5.5	8.4
	5	M	6.5	9.8
	6	M	6.3	8.5
	7	M	6.0	8.3
	8	M	6.6	10.6
	9	M	6.2	9.3
	10	M	6.1	8.9
	11	F	5.9	8.3
	12	F	5.6	8.5
	13	F	5.8	---
	14	F	6.0	---
	15	F	6.1	7.8
	16	F	5.9	8.1
	17	M	6.8	9.5
	18	F	5.6	8.5
	19	F	5.8	9.1
	20	F	5.8	8.3
64	1	M	6.0	9.0
	2	M	6.2	8.8
	3	M	6.7	9.6
	4	M	6.2	8.8
	5	F	6.5	9.3
	6	F	5.8	8.2
	7	F	5.7	7.5
	8	F	6.3	8.8
	9	F	6.1	8.8
	10	F	6.0	8.4
	11	F	6.1	8.7
	12	F	5.9	7.9
	13	F	6.3	8.8
	14	F	5.9	7.5
	15	F	5.7	8.3
	16	F	5.8	8.0
	17	F	6.0	8.2
	18	F	5.6	7.1
65	1	M	6.2	10.1
	2	M	5.5	8.1
	3	M	6.4	10.3
	4	M	6.3	9.7
	5	M	6.6	10.2
	6	M	5.7	9.3
	7	F	6.3	9.8
	8	F	6.2	10.2
	9	F	6.0	9.6
	10	F	6.0	9.3
	11	F	6.1	9.2
	12	F	6.1	9.3
	13	F	6.1	9.2
66	1	M	6.4	8.6
	2	M	6.5	8.0
	3	M	6.3	8.6
	4	M	6.5	7.9
	5	M	6.7	9.2
	6	M	6.7	8.9
	7	M	5.7	8.0
	8	M	6.3	8.5
	9	F	6.0	7.9
	10	F	5.8	7.8
	11	F	6.1	7.9
	12	F	6.3	8.1

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 3 (150 MG/KG)				
	13	F	5.0	6.1
	14	F	6.0	6.9
	15	F	5.6	7.2
	16	F	5.7	7.5
67	1	M	5.8	9.0
	2	M	6.2	9.3
	3	M	6.2	8.3
	4	M	6.2	8.6
	5	M	6.5	9.2
	6	M	6.6	10.1
	7	M	6.6	9.5
	8	F	5.8	8.4
	9	F	6.1	8.5
	10	F	6.6	10.0
	11	F	6.3	9.4
	12	F	6.4	8.7
	13	F	5.7	7.9
	14	F	5.1	--
	15	F	5.6	8.2
	16	F	5.8	7.4
	17	F	5.5	7.6
68	1	M	6.5	10.6
	2	M	5.8	--
	3	M	7.2	--
	4	M	7.1	11.1
	5	M	7.2	11.7
	6	M	7.1	9.6
	7	M	6.0	--
	8	M	7.6	12.3
	9	M	7.0	11.7
	10	M	7.1	10.0
	11	M	7.2	10.7
	12	F	6.9	11.0
	13	F	7.0	10.7
	14	F	6.5	9.4
	15	F	6.3	9.8
	16	F	5.2	8.1
	17	F	5.4	--
69	1	M	5.1	7.4
	2	M	5.8	7.8
	3	M	6.2	8.6
	4	M	6.3	9.2
	5	M	5.5	--
	6	M	6.0	--
	7	M	6.4	9.3
	8	F	5.3	7.8
	9	F	5.3	8.7
	10	F	5.2	7.7
	11	F	4.6	5.8
	12	F	6.2	9.8
	13	F	5.8	8.3
	14	F	5.4	7.9
	15	F	5.3	6.6
	16	F	5.3	7.7
	17	F	4.8	7.0
	18	F	5.5	7.0
70	1	M	6.6	8.7
	2	M	6.4	8.9
	3	M	5.9	7.9
	4	M	5.9	7.9
	5	M	6.0	8.2
	6	M	6.0	7.9
	7	M	6.0	8.6

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 3 (150 MG/KG)				
	8	M	5.9	7.1
	9	M	6.0	8.7
	10	M	--	--
	11	M	--	--
	12	F	6.0	8.3
	13	F	5.8	7.6
	14	M	6.3	8.0
	15	F	5.5	7.0
	16	F	5.7	8.2
	17	M	5.7	7.2
	18	F	5.4	6.8
	19	F	5.6	7.3
	20	F	--	--
GROUP 4 (500 MG/KG)				
71	1	M	7.9	12.0
	2	M	7.3	10.2
	3	F	6.5	9.7
	4	F	6.7	10.2
72	1	M	6.7	10.3
	2	M	5.0	7.9
	3	M	6.3	9.0
	4	M	6.4	9.5
	5	M	6.4	9.6
	6	F	6.6	10.2
	7	F	7.0	10.4
74	1	M	6.0	9.7
	2	M	5.4	7.8
	3	M	6.8	10.1
	4	M	6.9	11.2
	5	M	6.3	8.7
	6	F	6.5	9.3
	7	F	7.1	10.8
	8	F	6.9	10.7
	9	F	6.4	10.1
76	1	M	7.8	11.5
	2	M	7.4	10.9
	3	F	7.1	10.8
	4	F	7.1	10.4
	5	F	7.2	10.6
	6	F	7.0	10.0
	7	F	6.1	9.3
	8	F	5.1	7.8
78	1	M	5.7	8.5
	2	M	5.3	7.5
	3	M	5.5	--
	4	M	5.9	--
	5	M	5.8	--
	6	M	5.8	--
	7	F	5.6	7.3
	8	F	5.4	--
	9	F	5.4	--
	10	F	5.4	--
	11	F	5.3	--
79	1	M	--	
	2	M	--	
	3	M	--	
	4	F	5.4	
	5	F	5.3	

BODY WEIGHTS OF PUPS (GRAM)
F0-GENERATION - LACTATION

LITTER	PUP	SEX	DAY 1	DAY 4
GROUP 4 (500 MG/KG)				
80	1	M	6.9	10.8
	2	M	7.9	12.7
	3	M	6.1	8.8
	4	F	5.7	8.0
	5	F	6.6	9.8
	6	F	7.3	11.7
	7	F	7.3	11.6

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 1 (CONTROL)					
LITTER 41 17FEB2007	1	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	2	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	3	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	4	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	5	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	6	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	8	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	9	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	10	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	11	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	12	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	13	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	14	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	15	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	16	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	17	F	DAY 5 Planned Necropsy	FLC	No findings
				DAY 4	Small
				LLC	Small
				MACRO	No findings
	18	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
LITTER 42 16FEB2007	1	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	2	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	Small, no milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	M	DAY 5	Planned Necropsy	FLC	No findings
					DAY 4	Red spot neck
					LLC	No findings
					MACRO	No milk
	10	M	DAY 1	Dead at FLC	FLC	Dead
					MACRO	Cannibalism, no milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	17	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	18	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	19	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	20	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 43 14FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 1	Dead at FLC	FLC	Dead
					MACRO	No milk
	5	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	Red spot head
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	Red spot back
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 44 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No milk
LITTER 45 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 46 14FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	Red spot back
					LLC	No findings
					MACRO	No milk
LITTER 47 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	Red spot head
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 48 14FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	5	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	Small
	7	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	8	M	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	9	F	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	Small
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 6	Planned Necropsy	FLC	Small
					DAY 4	Small
					LLC	No findings
					MACRO	Small
	15	F	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	16	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 49 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 1 (CONTROL)						
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	17	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
GROUP 2 (50 MG/KG)						
LITTER 52 17FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 4	Spontaneous death	FLC	No findings
					LLC	Dead
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 53 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 6	Planned Necropsy	FLC	Red spot back
					LLC	No findings
					MACRO	No milk
	9	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	M	DAY 1	Dead at FLC	FLC	Dead
					MACRO	No milk
	14	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	17	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
	18	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	19	F	DAY 6	Planned Necropsy	FLC	Red spots back
					LLC	No findings
					MACRO	No milk
LITTER 54 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	17	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	18	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
LITTER 56 17FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 57 17FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 2	Missing	FLC	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 58 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	17	F	DAY 6	Planned Necropsy	FLC	Red spot back
					LLC	No findings
					MACRO	No milk
LITTER 59 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 60 14FEB2007	1	M	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannabalism
	2	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Missing
	3	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	5	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	6	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism, stomach not present

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 2 (50 MG/KG)						
	7	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	8	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	9	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	10	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	11	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism
	12	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Cannibalism, stomach not present
	13	F	DAY 1	Killed in extremis	FLC	No findings
					LLC	Cannibalism
					MACRO	Missing
GROUP 3 (150 MG/KG)						
LITTER 61 17FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	17	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 62 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 6	Missing	FLC	No findings
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 6	Planned Necropsy	FLC	Pale
					LLC	No findings
					MACRO	No findings
	14	F	DAY 6	Planned Necropsy	FLC	Pale
					LLC	No findings
					MACRO	No findings
LITTER 63 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 3	Missing	FLC	No findings
					LLC	Missing
	14	F	DAY 3	Missing	FLC	No findings
					LLC	Missing
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	17	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	18	F	DAY 5	Planned Necropsy	FLC	Red spot neck
					LLC	No findings
					MACRO	No milk
	19	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	20	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 64 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	6	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	17	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	18	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 65 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	6	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 66 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 67 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 3	Spontaneous death	FLC	Blue nose
					DAY 2	Blue nose
					LLC	Dead
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	17	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
LITTER 68 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 3	Missing	FLC	No findings
	3	M	DAY 3	Missing	FLC	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	M	DAY 5	Planned Necropsy	FLC	No findings
					DAY 3	Wound nose
					DAY 4	Scab nose
					LLC	Red nose
					MACRO	No milk
	7	M	DAY 4	Missing	FLC	No findings
	8	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	10	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	11	M	DAY 5	Planned Necropsy	FLC	Wound left hindleg
					DAY 2	Scab left hindleg
					DAY 3	Scab left hindleg
					DAY 4	Scab left hindleg
					LLC	Scab left hindleg
					MACRO	No milk
	12	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	13	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	14	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	15	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	16	F	DAY 5	Planned Necropsy	FLC	No findings
					DAY 4	Blue abdomen
					LLC	Blue abdomen
					MACRO	No milk
	17	F	DAY 3	Missing	FLC	No findings
LITTER 69 13FEB2007	1	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 3 (150 MG/KG)						
	4	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 4	Spontaneous death	FLC	Red spot nose
					LLC	No findings
					MACRO	No milk
	6	M	DAY 4	Missing	FLC	No findings
	7	M	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	9	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	10	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	11	F	DAY 6	Planned Necropsy	FLC	Small
					DAY 4	Small
					DAY 5	Small
					LLC	Small
					MACRO	No findings
	12	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	13	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	14	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	15	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	16	F	DAY 6	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	17	F	DAY 6	Planned Necropsy	FLC	Small
					LLC	No findings
					MACRO	No findings
	18	F	DAY 6	Planned Necropsy	FLC	Swelling head
					LLC	No findings
					MACRO	No findings
LITTER 70 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 3 (150 MG/KG)					
	6	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	7	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	8	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	9	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	10	M	DAY 1 Dead at FLC	FLC	Dead
				MACRO	No milk
	11	M	DAY 1 Dead at FLC	FLC	Dead
				MACRO	No milk
	12	F	DAY 5 Planned Necropsy	FLC	No findings
				DAY 2	Red nose
				DAY 3	Red nose, red spots tail
				DAY 4	Red tail apex
				LLC	Red tail apex
				MACRO	No milk
	13	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	14	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	15	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	16	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	17	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	18	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	19	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	20	F	DAY 1 Dead at FLC	FLC	Dead
				MACRO	No milk
GROUP 4 (500 MG/KG)					
LITTER 71 16FEB2007	1	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	2	M	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	3	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No milk
	4	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 4 (500 MG/KG)						
LITTER 72 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	Red spot back
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	Small
					DAY 2	Small
					DAY 3	Small
					DAY 4	Small
					LLC	Small
					MACRO	Small, no milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 74 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	Blue belly, no milk
					DAY 1	Blue abdomen
					DAY 2	Blue abdomen
					DAY 3	Blue abdomen
					LLC	No findings
					MACRO	No milk
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	9	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 76 16FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE		FINDINGS	
GROUP 4 (500 MG/KG)						
	3	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	4	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	5	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	6	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No milk
	8	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
LITTER 78 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 2	Missing	FLC	No findings
	4	M	DAY 2	Missing	FLC	No findings
	5	M	DAY 2	Missing	FLC	No findings
	6	M	DAY 2	Missing	FLC	Weak, blue
	7	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	8	F	DAY 2	Missing	FLC	No findings
	9	F	DAY 2	Missing	FLC	No findings
	10	F	DAY 2	Missing	FLC	No findings
	11	F	DAY 2	Missing	FLC	Weak, blue
LITTER 79 15FEB2007	1	M	DAY 1	Dead at FLC	FLC	No findings
					MACRO	No milk
	2	M	DAY 1	Dead at FLC	FLC	No findings
					MACRO	No milk
	3	M	DAY 1	Dead at FLC	FLC	Dead
					MACRO	No milk
	4	F	DAY 2	Spontaneous death	FLC	No findings
					LLC	Dead
					MACRO	No milk
	5	F	DAY 2	Spontaneous death	FLC	No findings
					LLC	Dead
					MACRO	No milk
LITTER 80 15FEB2007	1	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	2	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	3	M	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings
	4	F	DAY 5	Planned Necropsy	FLC	No findings
					LLC	No findings
					MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

INDIVIDUAL PUP DATA
F0-GENERATION - LACTATION

LITTER DELIVERY	PUP		END OF P.P. PHASE	FINDINGS	
GROUP 4 (500 MG/KG)					
	5	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	6	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings
	7	F	DAY 5 Planned Necropsy	FLC	No findings
				LLC	No findings
				MACRO	No findings

FLC - FIRST LITTER CHECK, DAY P.P. - CLINICAL SIGNS ,
LLC - LAST LITTER CHECK, MACRO - MACROSCOPIC FINDINGS

KEY TO MISSING VALUES AND REMARKS CLINICAL LABORATORY INVESTIGATIONS

End of Treatment

Haematology:		
Animal(s):		
2, 6, 36, 52, 53, 58		Differential leucocyte count was also performed manually because of an abnormal plot in the automated count and these results are reported

Clinical Biochemistry: No remarks

APPENDIX 3

ANALYTICAL REPORT

Author

Dr. Ir. E. Baltussen

Completion date analytical study

\\

Laboratory Project Identification

NOTOX Project 479003
NOTOX Substance 170676/A

1. CONTENTS

TABLES

FIGURES

2. REPORT APPROVAL

PRINCIPAL SCIENTIST: Dr. Ir. E. Baltussen
(Analytical Chemistry)

.....

Date:

3. SUMMARY

The purpose of this part of the study was to determine the accuracy of preparation, homogeneity and stability of the test substance in formulations.

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. between 90% and 110%).

Small test substance peaks were observed in one of the two samples of the Group 1 formulation. The maximum contribution to the other samples of Groups 2-4 is 0.15% based on area. This was due to carry-over in the analytical system. In the second sample of the Group 1 formulation no test substance peaks were observed. Therefore it was concluded that Group 1 did not contain any test substance.

The formulations of Group 2 and Group 4 were homogeneous (i.e. coefficient of variation < 10%).

Formulations at the entire range were stable for at least 5 hours when stored at room temperature.

4. INTRODUCTION

4.1. Preface

Study plan (analytical study)	Start	: 08 January 2007
	Completion	: 09 January 2007

4.2. Aim of the study

The purpose of the analytical study was to determine the accuracy of preparation, homogeneity and stability of the test substance in formulations.

5. MATERIALS AND METHODS

5.1. Reagents

Milli-Q water	Tap water purified by a Milli-Q water purification system (Millipore, Bedford, MA, USA)

5.2. Samples

Accuracy, homogeneity and stability were determined for formulations prepared for use on day 1.

Duplicate samples (approximately 1000 µl), which were taken from the formulations, were pipetted in a HPLC-vial. For determination of accuracy, samples were taken at 50% height or at 90%, 50% and 10% height. The latter set of samples was also used for the determination of the homogeneity of the formulations. For determination of stability, additional samples were taken at 50% height [1].

5.3. Analytical method

The chromatogram of the test substance solution showed two test substance peaks. The sum of the area of these peaks was used as response in the calculations.

5.3.1. Analytical conditions

Quantitative analysis was based on the analytical method validated for the test substance during NOTOX project 479025.

Analytical conditions:

Instrument	Gas chromatograph 6890N (Agilent Technologies, Palo Alto, CA, USA)
Injector	CombiPal (CTC analytics, Zwingen, Zwitserland)
Detector	Flame ionisation detector (Agilent Technologies)
Column	CP-Volamine; 30 m × 320 µm i.d. (Varian, Middelburg, The Netherlands)
Carrier gas	helium
Carrier gas flow	2 ml/min
Injection	Programmed temperature vaporizer (PTV)
PTV Mode	Split
Split ratio	100
Split flow	200 ml/min
Injection volume	1 µl

[1] Because at t=0 samples were taken at 10% 50%, and 90% height, the mean concentration of these samples was used as t=0 value for calculation of stability.

PTV temperature program

Initial temperature	60°C
Initial time	0.1 min
Rate	600 °C/min
Final temperature	280 °C
Hold time	10 min

Oven temperature program

Initial temperature	40 °C
Rate	20 °C/min
Temperature	265 °C
Hold time	5 min

FID detection

Temperature	300°C
Hydrogen	40 ml/min
Air	450 ml/min
Nitrogen (make-up)	50 ml/min

5.3.2. Preparation of the calibration solutions

Stock- and spiking solutions
Stock- and spiking solutions of the test substance were prepared in Milli-Q water at concentrations of 14.5 – 49.6 g/l.

Calibration solutions
Calibration solutions in the concentration range 1.00 – 49.6 g/l were prepared from two stock solutions. The end solution of the calibration solutions was Milli-Q water.

Procedural recovery samples
Approximately 1000 mg blank vehicle was spiked with the test substance at a nominal concentration of 2.5 or 25 mg/ml. The accuracy samples were treated similarly as described in paragraph 5.2 'Samples'.

Note: the spiking volume was > 5% (v/v) of the sample volume. Nominal concentrations were corrected for the spiking volume.

5.3.3. Sample injections

Calibration solutions were injected in duplicate. Test samples and procedural recovery samples were analysed by single injection.

5.4. Electronic data capture

System control, data acquisition and data processing were performed using the following programme:
- Empower version 5.00 (Waters, Milford, MA, USA).

5.5. Formulas

Response (R) — Peak area test substance [units]

Calibration curve — $R = a\,C_N + b$

where:
C_N = nominal concentration [mg/l]
a = slope [units × l/mg]
b = intercept [units]

Analysed concentration (C_A) — $C_A = \frac{(R-b)}{a}$ [mg/ml]

Recovery — $\frac{C_A}{C_N} \times 100\%$

where:
C_N = nominal concentration [mg/ml]

Accuracy — $\frac{C_A}{C_T} \times 100\%$

where:
C_T = target concentration [mg/ml]

Relative difference (relative diff.) — $\frac{C_t - C_0}{C_0} \times 100\%$

where:
C_t = mean concentration of stored samples [mg/ml]
C_0 = mean concentration of non-stored samples [mg/ml]

5.6. Specifications

Preparation of formulations was considered acceptable if the measured concentration levels were between 90% and 110% of the target concentrations and if the coefficient of variation was < 10%. Formulations were considered to be stable if the relative difference between the stored and freshly taken samples was < 10%.

6. RESULTS

6.1. Calibration curves

A calibration curve was constructed using four concentrations. For each concentration, two responses were used. Linear regression analysis was performed using the least squares method with a 1/concentration^2 weighting factor. The coefficient of correlation (r) was > 0.99.

HPLC chromatograms of a test substance solution and blank solution are shown in Figure 1. In the blank solution small test substance peaks were observed, this was due to carry-over in the analytical system.

6.2. Samples

6.2.1. Procedural recovery samples

The results for the procedural recovery samples are given in Table 1.

Mean recoveries of the procedural recovery samples were between 93% and 100%. Because the criterion that mean recoveries should be between 70% and 110% was met, the results for the test samples were accepted.

6.2.2. Test samples

The results of the test samples are given in Tables 2 and 3. Figure 2 shows GC chromatograms of samples from Group 1, Group 2, Group 3 and Group 4 taken at 50% height.

The concentrations analysed in the formulations of Group 2, Group 3 and Group 4 were in agreement with target concentrations (i.e. between 93% and 105%).

Small test substance peaks were observed in one of the two samples of the Group 1 formulation. The maximum contribution to the other samples of Groups 2-4 is 0.15% based on area. This was due to carry-over in the analytical system. In the second sample of the Group 1 formulation no test substance peaks were observed. Therefore it was concluded that Group 1 did not contain any test substance.

The formulations of Group 2 and Group 4 were homogeneous (2.5% and 3.3% relative standard deviation, respectively).

Analysis of Group 2 and Group 4 formulations after 5 hours of storage at room temperature yielded a relative difference of –2.5% and –1.5%, respectively. Therefore, the samples were considered stable at room temperature for at least at 5 hours.

TABLES

Table 1 Procedural recovery samples

Date of preparation [dd-mm-yy]	Date of analysis [dd-mm-yy]	Concentration nominal [mg/ml]	Concentration analysed [mg/ml]	Recovery [%]	Mean recovery [%]
08-01-07	08-01-07	2.36 2.36	2.20 2.26	93 96	95
08-01-07	08-01-07	26.5 22.6	25.4 22.6	96 100	98

Table 2 Accuracy and homogeneity test for the formulations

Group	Date of analysis [dd-mm-yy]	Sample position	Concentration [mg/ml]		Accuracy [%]	Homogeneity (coefficient of variation) [%]
			Target	Analysed		
1	08-01-07	50% height	0.00	[1] n.d.	[1] n.a.	
2	08-01-07	90% height	2.50	2.39 2.47	96 99	
		50% height	2.50	2.40 2.32	96 93	2.5
		10% height	2.50	2.33 2.32	93 93	
3	08-01-07	50% height	7.50	7.22 7.06	96 94	
4	08-01-07	90% height	25.0	24.3 24.8	97 99	
		50% height	25.0	26.2 24.3	105 97	3.3
		10% height	25.0	25.4 24.0	102 96	

n.d. Not detected.

n.a. Not applicable.

[1] A peak was observed at the test substance position, the maximum contribution to the samples of Groups 2-4 was 0.15% based on area.

Table 3 Stability test for the formulations prepared

Group	Date of analysis [dd-mm-yy]	Concentration analysed [mg/ml]		Relative diff. [%]
		t=0 [1]	t=5 hours	
2	08-01-07	2.37	2.31 [2]	-2.5
4	08-01-07	24.8	24.5 [3]	-1.5

[1] Mean of six samples at t=0 taken at 10%, 50% and 90% height. For individual results see Table 2.

[2] Mean of two samples at t=5 hours taken at 50% height. Individual results were 2.30 and 2.32 mg/ml.

[3] Mean of two samples at t=5 hours taken at 50% height. Individual results were 24.8 and 24.1 mg/ml.

FIGURES

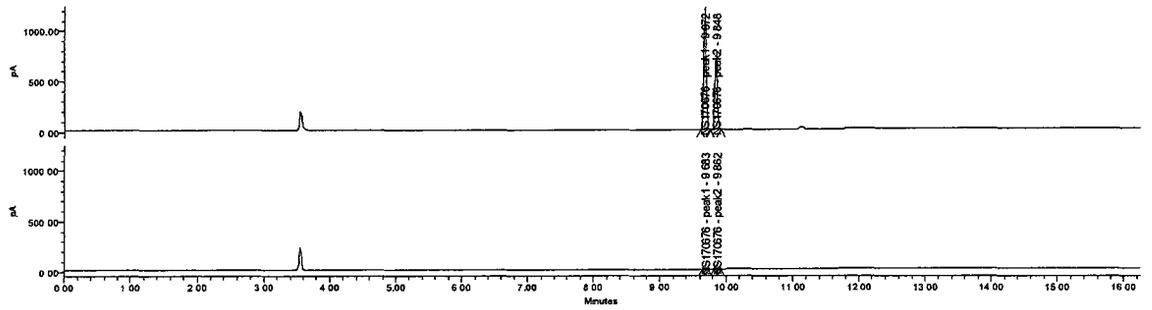

Figure 1 **GC chromatograms of a 49.6 mg/l calibration solution [top; res. id. 1151] and blank Milli-Q water [bottom; res. id. 1314].**

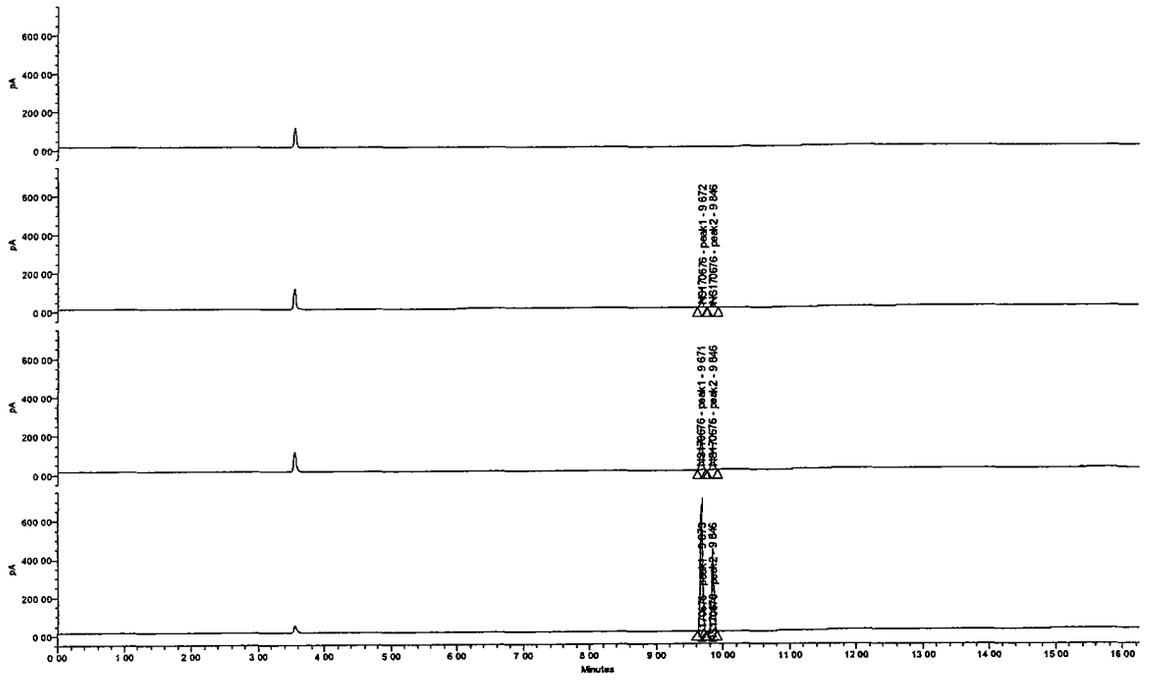

Figure 2 **GC chromatograms from top to bottom of samples from Group 1 [res. id. 1316], Group 2 [res. id. 1279], Group 3 [res. id. 1319] and Group 4 [res. id. 1291].**

ProPath GmbH

APPENDIX 4

Draft Pathology Report

Combined 28-Day Repeated Dose Toxicity Study with the

Reproduction/Developmental Toxicity

Screening Test of Dytek® DCH-99

in Rats by Oral Gavage

NOTOX Project 479003
NOTOX Substance 170676/A

This report contains 92 pages

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Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

NOTOX no. : 479003
Propath no. : 07014
Date : 23.May.2007

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Test item	: Dytek® DCH-99	NOTOX no.	: 479003
Test System	: Combined Repro/Tox Screening Test by Gavage in Rats	Propath no.	: 07014
Sponsor	: Invista S.a.r.l.	Date	: 23.May.2007

Statement of Compliance

The undersigned hereby declares, that the histopathology data in this report were compiled by him, and that they reflect accurately the primary data records. This report, consisting of 92 pages, was created by the computer system of Propath GmbH.

This study phase was conducted in compliance with:

Swiss Ordinance relating to Good Laboratory Practice, adopted May 18th, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26th, 1997 by decision of the OECD Council [C(97)186/Final].

which essentially conform to:

The United States Food and Drug Administration Good Laboratory Practice Regulations and

The United States Environmental Protection Agency Good Laboratory Practice Regulations.

Jeffrey Th. Wilson, Dr.med.vet, BVSc, MSc, MRCVS
Principal Investigator - Toxicologic Pathologist

Date:

Propath GmbH
CH-4133 Pratteln, Switzerland

Test item : Dytek® DCH-99
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Quality Assurance Statement

The facilities of Propath GmbH are periodically (4x/year) inspected by the Quality Assurance Unit (CERTUS Quality Assurance Services GmbH). This report was inspected by the Quality Assurance Unit (CERTUS).

The respective dates are given below:

Inspection type	Date(s) of inspection	Date(s) of reporting
Facility based inspection (latest):	26.04.2007	26.04.2007
Report inspection:		

The findings were reported to the test facility (Propath) management (only inspection of test facility (test site) Propath), the principal investigator, the study director, the management of the test facility of the study director and the "lead QA".

The methods, procedures and observations described were found to be accurately described and the reported results to reflect the raw data.

A. Brüggen
QA Inspector

Date:

CERTUS Quality Assurance Services GmbH
CH-4125 Riehen, Switzerland
QAU of Propath GmbH

Summary

Pathomorphologic examination was performed on 80 Wistar rats (40 males, 40 females) which had been subjected to a combined repeated dose toxicity study with reproduction/developmental toxicity screening test, with the test item **Dytek® DCH-99**.

The rats were assigned to four dose groups each containing ten males and ten females. The test item was administered once daily by gavage at doses of 50, 150 and 500 mg/kg (dose groups 2, 3 and 4 respectively) for 2 weeks prior to mating, during mating and up to the day prior to necropsy – at least a total of 28 days dosing. The rats of the control group 1 received the vehicle, water (milli U), alone.

All rats were necropsied. Histopathologic examination was performed on an extensive list of organs and tissues from five males and five females of groups 1 and 4, as well as ***adrenal glands*** (males), ***kidneys***, ***liver***, ***lungs*** and ***thymus*** from groups 2 and 3 and gross lesions from all rats. In addition the reproductive organs of animals suspected of infertility were also examined. Sections of testes from five group 1 and 4 rats were assessed for spermatogenesis staging.

There were no unscheduled deaths.

At necropsy *pale discolouration* of the ***liver*** was noted in five group 4 (500 mg/kg/day) males.

Treatment related morphological alterations were recorded in several organs

In the ***lungs***, *alveolar macrophage foci* were increased in incidence and severity to moderate in group 4 females ($p < 0.05$). In the same organ *lymphocytic alveolar inflammation* was slightly increased in incidence (positive trend $p < 0.05$) in males and in incidence and severity to moderate in females ($p < 0.05$).

In the ***liver***, *hepatocellular vacuolation* at a minimal or slight degree was seen in four group 4 males and in three group 4 females. This incidence did not reach statistical significance in either sex, however there was a positive trend (p at least < 0.05) for both sexes.

In the ***adrenal glands*** of males *vacuolation in the zona fasiculata* at minor degrees of severity was slightly increased in incidence in group 4 which was not significant. However there was a positive trend ($p < 0.05$).

These findings were chiefly minor in nature and may be regarded as either slight increases in spontaneously occurring conditions or adaptive. As such they were considered to be indicators of slight toxicity to the test-item. From a toxicological standpoint the NOAEL may be regarded as 150 mg/kg/day.

In male animals suspected of infertility: one control versus seven treated (groups 2 and 4) there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. Further, the spermatogenic staging profiles were normal for all group 1 and group 4 males evaluated.

From a total of seven treated females (groups 2 and 4) compared to one control examined for suspected infertility, there was evidence suggestive of foetal loss in three and evidence of oestrus cycle disturbance in a further two. The remaining two had uterine implantation sites. No adverse morphological alterations were noted in the reproductive organs of the one control animal. These findings indicate that in females, treatment with the test compound may have had an adverse affect on the animals reproductive performance.

Materials and Methods

Study Design

Dose group	Dose mg/kg/day	Number of rats		Animal numbers	
	Dytek® DCH-99	F_0 males	F_0 females	males	females
1	0	10	10	1 – 10	41 – 50
2	50	10	10	11 – 20	51 – 60
3	150	10	10	21 – 30	61 – 70
4	500	10	10	31 – 40	71 – 80

Administration of the Test Item

The test item was administered once daily by gavage for 2 weeks prior to mating, during mating and up to the day prior to necropsy – at least a total of 28 days dosing. Rats of the control group 1 received the vehicle, water (milli U), alone.

Necropsy and Histopathology

At the end of the assigned study period, the rats were killed by exsanguination following anesthesia by isoflurane. Complete necropsies were performed on all rats. From 5 selected surviving animals per sex and group:

	males:	*females*
Group 1	1, 2, 4, 6, 7	42, 44, 45, 47, 48
Group 2	12, 13, 14, 16, 17	52, 53, 54, 58, 59
Group 3	21, 22, 23, 24, 25	62, 63, 64, 66, 70
Group 4	31, 32, 34, 35, 36	71, 72, 78, 79, 80

representative tissue samples of the following organs were preserved in 4% phosphate buffered neutral formaldehyde solution (10% formalin). Testes, epididymides, eyes, optic nerves and Harderian glands were initially fixed in Davidson's solution. Organs listed in ***bolded italics*** were sampled and fixed from all animals.

> Adrenal glands, aorta, bone – sternum [and femur including joint]; bone marrow - sternal, brain, ***clitoral glands***, ***epididymides***, esophagus, [eyes with optic nerve and Harderian glands]; heart, [identification marks], ***kidneys***, [lacrimal glands - exorbital], large intestine - cecum, colon and rectum; [larynx], ***liver***, lungs, lymph nodes - mandibular and mesenteric ; [female mammary gland area], [nasopharynx], ***ovaries***, pancreas, pituitary gland, ***preputial glands***, ***prostate gland***, [salivary glands – mandibular and sublingual]; sciatic nerve, ***seminal vesicles with coagulation glands***, [skeletal muscle], [skin], small intestine - duodenum, jejunum and ileum with Peyer's patches; spinal cord - cervical, midthoracic and lumbar; spleen, ***stomach***, ***testes***, thymus, thyroid glands with parathyroid glands, [tongue], trachea, urinary bladder, ***uterus with uterine cervix***, ***vagina*** and all organs or tissues with ***macroscopic abnormalities***.

Following fixation, organs (except those listed in brackets) from the selected animals of groups 1 and 4, along with all organs or tissues with macroscopic abnormalities from all rats, were trimmed, processed and embedded in paraffin wax. Sections were cut at a thickness of 2-4 micrometers and stained with hematoxylin and eosin.

Materials and Methods

Following examination of these tissues, sections of ***adrenal glands*** (males), ***kidneys***, ***liver***, ***lungs*** and ***thymus*** from the above listed 5 selected animals of the intermediate dose groups 2 and 3 were prepared and examined:

Extra sections of testes stained by the PAS method from the selected males of groups 1 and 4 were prepared for spermatogenesis staging.

From animals suspected of infertility:

	males:	*females*
Group 1	10	50
Group 2	11, 15, 20	51, 55, 60
Group 3	-	-
Group 4	33, 35, 37, 39	73, 75, 77, 79

sections were prepared from the reproductive organs.

The sections were examined by light microscopy in April/May, 2007.

Data Compilation

The animal data and macroscopic findings were electronically transferred from the necropsy raw data files of NOTOX into the computer system of Propath GmbH where the microscopic findings were recorded by the undersigned pathologist using on-line input.

Macroscopic findings are presented in summary in Table 1 - Incidence All Macroscopic Findings and in full descriptive terms in Table 7 - Individual Animal Data Records. Wherever possible, macroscopic findings were correlated with a microscopic finding.

Microscopic findings are listed for each animal along with severity grades in Table 5 - Individual Animal Microscopic Findings and summarized in Table 2 - Incidence – Selected Microscopic Findings with Grades and Table 4 - Incidence All Microscopic Findings. They are further given in full descriptive terms in Table 7 - Individual Animal Data Records. Histologic changes were described according to their distribution and morphologic character and were graded for severity on a scale of 1 – 5 (see key Table 5 - Individual Animal Microscopic Findings). The results of spermatogenesis staging are presented in Table 8 - Staging of Spermatogenesis.

Statistical analyses of selected microscopic findings are listed in Table 3 - Statistical Analyses Selected Microscopic Findings.

Archiving

The final pathology report (original hardcopy), all histologic slides, dispatch list(s) and a copy of the electronic records and final pathology report as captured by the appropriate software (on CD-ROM) will be sent to NOTOX B.V. to archive. Any other documents and electronic data covered by GLP, will be archived by Propath GmbH according to company standard operating procedures.

Results

Mortality

There were no unscheduled deaths.

Macroscopic Findings

Discolouration, pale of the ***liver*** was noted in five group 4 (500 mg/kg/day) males. The remaining macroscopic findings were considered to be spontaneous in nature and did not distinguish treated animals from the controls.

Microscopic Findings

In the ***lungs***, *alveolar macrophage foci* were noted at a minimal degree in one group 3 (150 mg/kg/day) and at a slight degree in one group 4 male animals. In females this finding was present at a slight degree of severity in one group 1 (0 mg/kg/day, control) and at slight or moderate severity in five group 4 animals which was significantly increased ($p < 0.05$). In the same organ *lymphocytic alveolar inflammation* was recorded at a slight degree in one group 1, minimal in one group 3 and also at a minimal degree in four group 4 males. In females, one animal in each of groups 1, 2 (50 mg/kg/day) and 3 recorded this finding at a minimal degree and in group 4, five animals at minimal to moderate degree. Again this was significantly increased in group 4 females ($p < 0.05$) and there was a positive trend ($p < 0.05$) in males.

In the ***liver***, *hepatocellular vacuolation* at a minimal or slight degree was seen in four group 4 males and in three group 4 females. This incidence did not reach statistical significance in either sex, however there was a positive trend (p at least <0.05) for both sexes. This finding was the microscopic correlate to the pale discolouration in this organ noted at necropsy.

Corticomedullary tubular basophilia at a minimal or slight degree was recorded in the ***kidneys*** of males: two in group 1, one in group 3 and two in group 4; in females: one in group 1 and three in groups 2 and 4. This was neither significantly increased or positive in trend for either sex.

In the ***adrenal glands*** of males *vacuolation in the zona fasiculata* was seen at a minimal degree in two group one, two group 2, slight degree in one group 3 and at minimal or slight degree in four group 4 animals. This slight increase in group 4 was not significant, however again there was a positive trend ($p < 0.05$).

Lymphoid atrophy – involution of the ***thymus*** was recorded in males: at minimal degree one group 1, slight in one group 3 and slight in two group 4 animals; in females: at minimal to moderate in four group 1, minimal in one group 3 and slight or moderate in three group 4 animals. This was neither significantly increased or positive in trend for either sex.

In male animals suspected of infertility there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. In the females *implantation sites* were in evidence in animals 60 (group 2) and 79 (group 4). Animal 51 (group 2) exhibited *endometrial squamous metaplasia,* animal 55 (group 2) had a *deciduoma* and animal 75 (group 4) had *endometrial inflammation.* These latter findings may be considered as evidence for foetal loss. Animals 73 and 77 (group 4) had vaginal *epithelial mucification* (possible oestrus cycle disturbance). In animal 50 (control) there were no findings to account for infertility.

Results

The spermatogenic staging profiles were normal for all group 1 and group 4 males evaluated.

The remainder of the recorded microscopic findings were within the range of background pathology encountered in Wistar rats of this age and occurred at similar incidences and severity in both control and treated rats.

Conclusions

Following the administration of **Dytek® DCH-99** by once daily gavage to Wistar rats at doses up to 500 mg/kg for 2 weeks prior to mating, during mating and up to the day prior to necropsy – at least a total of 28 days dosing, there were some minor morphological alterations in several organs.

In the ***lungs***, *alveolar macrophage foci* were increased in incidence and severity to moderate in group 4 females ($p < 0.05$). In the same organ *lymphocytic alveolar inflammation* was slightly increased in incidence (positive trend $p < 0.05$) in males and in incidence and severity to moderate in females ($p < 0.05$).

In the ***liver***, *hepatocellular vacuolation* at a minimal or slight degree was seen in four group 4 males and in three group 4 females. This incidence did not reach statistical significance in either sex, however there was a positive trend (p at least < 0.05) for both sexes.

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These findings were chiefly minor in nature and may be regarded as either slight increases in spontaneously occurring conditions or adaptive. As such they were considered to be indicators of slight toxicity to the test-item. From a toxicological standpoint the NOAEL may be regarded as 150 mg/kg/day.

In male animals suspected of infertility: one control versus seven treated (groups 2 and 4) there were no findings in the reproductive organs of any of the animals which would account for poor reproductive performance. Further, the spermatogenic staging profiles were normal for all group 1 and group 4 males evaluated.

From a total of seven treated females (groups 2 and 4) compared to one control examined for suspected infertility, there was evidence suggestive of foetal loss in three and evidence of oestrus cycle disturbance in a further two. The remaining two had uterine implantation sites. No adverse morphological alterations were noted in the reproductive organs of the one control animal. These findings indicate that in females, treatment with the test compound may have had an adverse affect on the animals reproductive performance.

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

NOTOX no. : 479003
Propath no. : 07014
Date : 23.May.2007

Table 1 Incidence All Macroscopic Findings

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Lungs								
Focus/foci	0	0	0	0	0	0	0	4
Stomach								
Reddish contents	0	0	0	0	0	1	0	0
Liver								
Discolouration	0	0	0	5	0	0	0	0
Diaphragmatic hernia	0	0	0	0	0	0	1	0
Kidneys								
Pelvic dilation	1	0	0	0	0	0	0	0
Seminal vesicles								
Reduced in size	0	1	1	0				
Uterus								
Contains fluid					0	1	0	0
Enlarged					0	1	0	0
Cervix								
Enlarged					0	1	0	0
Adrenal glands								
Enlarged	0	0	0	0	0	1	0	0
Mandibular lymph nodes								
Discolouration	0	0	0	0	2	0	0	1
Skin								
Alopecia	0	0	0	0	0	1	0	0
Bone								
Bent	1	1	0	0	0	0	0	0

Table 2 Incidence – Selected Microscopic Findings with Grades

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Lungs								
number examined	5	5	5	5	5	5	5	5
Alveolar macrophage foci								
(minimal)	0	0	1	0	0	0	0	0
(slight)	0	0	0	1	1	0	0	3
(moderate)	0	0	0	0	0	0	0	2
Total	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**5**
Alveolar inflammation, lymphocytic								
(minimal)	0	0	1	4	1	1	1	1
(slight)	1	0	0	0	0	0	0	2
(moderate)	0	0	0	0	0	0	0	2
Total	**1**	**0**	**1**	**4**	**1**	**1**	**1**	**5**
Liver								
number examined	5	5	5	7	5	5	5	5
Hepatocellular vacuolation								
(minimal)	0	0	0	3	0	0	0	2
(slight)	0	0	0	1	0	0	0	1
Total	**0**	**0**	**0**	**4**	**0**	**0**	**0**	**3**

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Table 2 Incidence – Selected Microscopic Findings with Grades

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Kidneys								
number examined	6	5	5	5	5	5	5	5
Tubular basophilia, corticomedullary								
(minimal)	2	0	1	2	1	2	0	3
(slight)	0	0	0	0	0	1	0	0
Total	**2**	**0**	**1**	**2**	**1**	**3**	**0**	**3**
Adrenal Glands								
number examined	5	5	5	5	5	1		5
Vacuolation, multifocal in z. fasiculata								
(minimal)	2	2	0	1	0	0		0
(slight)	0	0	1	3	0	0		0
Total	**2**	**2**	**1**	**4**	**0**	**0**		**0**
Thymus								
number examined	5	5	5	5	5	5	5	5
Lymphoid atrophy - involution								
(minimal)	1	0	0	0	1	0	1	0
(slight)	0	0	1	2	2	0	0	2
(moderate)	0	0	0	0	1	0	0	1
Total	**1**	**0**	**1**	**2**	**4**	**0**	**1**	**3**

Test item : Dytek® DCH-99 NOTOX no. : 479003
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Table 3 Statistical Analyses Selected Microscopic Findings

DOSE GROUP:		1	2	3	4	Trend
Lungs						
Alveolar macrophage foci						
Male	n	0	0	1	1	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	0	0	1	2	
	Ex P		N.S.	N.S.	N.S.	N.S.
	KW P		N.S.	N.S.	N.S.	N.S.
Female	n	1	0	0	5	
	N	5	5	5	5	
	Min	0	0	0	2	
	Max	2	0	0	3	
	Ex P		N.S.	N.S.	+	+++
	KW P		N.S.	N.S.	(+)	+++
Lungs						
Alveolar inflammation, lymphocytic						
Male	n	1	0	1	4	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	2	0	1	1	
	Ex P		N.S.	N.S.	N.S.	+
	KW P		N.S.	N.S.	N.S.	+
Female	n	1	1	1	5	
	N	5	5	5	5	
	Min	0	0	0	1	
	Max	1	1	1	3	
	Ex P		N.S.	N.S.	+	++
	KW P		N.S.	N.S.	+	+++
Liver						
Hepatocellular vacuolation						
Male	n	0	0	0	4	
	N	5	5	5	7	
	Min	0	0	0	0	
	Max	0	0	0	2	
	Ex P		N.S.	N.S.	N.S.	++
	KW P		N.S.	N.S.	N.S.	++
Female	n	0	0	0	3	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	0	0	0	2	
	Ex P		N.S.	N.S.	N.S.	+
	KW P		N.S.	N.S.	N.S.	++

n = number affected
Min = minimum grade
Ex = Fisher's exact
P = probability value
(+) = p <0.1
++ = p <0.01

N= number in sample
Max = maximum grade
KW = Kruskal-Wallis
N.S = p not significant
+ = p <0.05
+++ = p <0.001

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Table 3 Statistical Analyses Selected Microscopic Findings

DOSE GROUP:		1	2	3	4	Trend
Kidneys						
Tubular basophilia, corticomedullary						
Male	n	2	0	1	2	
	N	6	5	5	5	
	Min	0	0	0	0	
	Max	1	0	1	1	
	Ex P		N.S.	N.S.	N.S.	N.S.
	KW P		N.S.	N.S.	N.S.	N.S.
Female	n	1	3	0	3	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	1	2	0	1	
	Ex P		N.S.	N.S.	N.S.	N.S.
	KW P		N.S.	N.S.	N.S.	N.S.
Adrenal Glands						
Vacuolation, multifocal in z. fasiculata						
Male	n	2	2	1	4	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	1	1	2	2	
	Ex P		N.S.	N.S.	N.S.	N.S.
	KW P		N.S.	N.S.	N.S.	+

n = number affected
Min = minimum grade
Ex = Fisher's exact
P = probability value
(+) = p <0.1
++ = p <0.01

N= number in sample
Max = maximum grade
KW = Kruskal-Wallis
N.S = p not significant
+ = p <0.05
+++ = p <0.001

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

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Table 3 Statistical Analyses Selected Microscopic Findings

DOSE GROUP:		1	2	3	4	Trend
Thymus						
Lymphoid atrophy - involution						
Male	n	1	0	1	2	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	1	0	2	2	
	Ex P		N.S.	N.S.	N.S.	N.S.
	KW P		N.S.	N.S.	N.S.	N.S.
Female	n	4	0	1	3	
	N	5	5	5	5	
	Min	0	0	0	0	
	Max	3	0	1	3	
	Ex P		-	N.S.	N.S.	N.S.
	KW P		(-)	N.S.	N.S.	N.S.

n = number affected
Min = minimum grade
Ex = Fisher's exact
P = probability value
(+) = p <0.1
++ = p <0.01

N= number in sample
Max = maximum grade
KW = Kruskal-Wallis
N.S = p not significant
+ = p <0.05
+++ = p <0.001

Test item : Dytek® DCH-99
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Table 4 Incidence All Microscopic Findings

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Brain								
number examined	5			5	5			5
Spinal Cord - cervical								
number examined	5			5	5			5
Spinal Cord - midthoracic								
number examined	5			5	5			5
Spinal Cord - lumbar								
number examined	5			5	5			5
Axonal swelling, focal	0			0	2			0
Sciatic Nerve								
number examined	5			5	5			5
Myelin fragmentation	2			3	0			0
Heart								
number examined	5			5	5			5
Inflammation, lymphoid	0			0	0			1
Myofiber necrosis	0			0	0			1
Aorta								
number examined	5			5	5			5
Trachea								
number examined	5			5	5			5
Lungs								
number examined	5	5	5	5	5	5	5	5
Alveolar macrophage foci	0	0	1	1	1	0	0	5
Alveolar inflammation, lymphocytic	1	0	1	4	1	1	1	5

Test item : Dytek® DCH-99
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Table 4 Incidence All Microscopic Findings

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Lungs								
Peri- vascular/bronchial, inflammatory cell foci	2	0	0	1	0	0	0	0
Lymphoid hyperplasia (BALT)	2	1	0	0	0	0	0	0
Osseous metaplasia	0	1	1	0	0	1	0	0
Esophagus								
number examined	5			5	5			5
Myodegeneration, focal	2			0	2			0
Stomach								
number examined	5			5	5	1		5
Dilated gastric pits	0			0	1	0		2
Duodenum								
number examined	5			5	5			5
Jejunum								
number examined	5			5	5			5
Ileum								
number examined	5			5	5			5
Peyer's Patches (GALT)								
number examined	5			5	5			5
Cecum								
number examined	5			5	5			5
Colon								
number examined	5			5	5			5
Rectum								
number examined	5			5	5			5

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
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Table 4 Incidence All Microscopic Findings

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Liver								
number examined	5	5	5	7	5	5	5	5
Hepatodiaphragmatic nodule	0	0	0	0	0	0	1	0
Inflammation, granulocytic/ mononuclear	5	5	5	6	4	4	2	3
Hepatocellular vacuolation	0	0	0	4	0	0	0	3
Hematopoietic cell foci	0	0	1	0	1	0	1	1
Pancreas								
number examined	5			5	5			5
Exocrine atrophy, focal	0			1	0			0
Kidneys								
number examined	6	5	5	5	5	5	5	5
Pelvic dilation	1	0	0	0	0	0	0	0
Hyaline cast(s)	2	0	0	1	0	2	0	1
Inflammation, lymphoid	0	1	1	0	1	2	0	0
Tubular basophilia, outer stripe medulla, diffuse	0	1	0	0	0	0	0	0
Tubular basophilia, corticomedullary	2	0	1	2	1	3	0	3
Urinary Bladder								
number examined	5			5	5			5
Testes								
number examined	6	3		8				
Epididymides								
number examined	6	3		8				

Table 4 Incidence All Microscopic Findings

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Prostate Gland								
number examined	6	3		8				
Inflammation, lymphoid	1	0		0				
Seminal Vesicles								
number examined	6	3	1	8				
Acinar atrophy, diffuse	0	0	0	1				
Coagulating Glands								
number examined	6	3	1	8				
Acinar atrophy, diffuse	0	0	0	1				
Preputial Glands								
number examined	5			5				
Cystic duct, inspissated contents	2			0				
Ovaries								
number examined					6	3		9
Uterus								
number examined					6	3		9
Implantation site(s)					5	1		6
Inflammation, granulocytic/ lymphocytic					0	1		1
Estrus epithelium					1	0		0
Deciduoma					0	1		0
Uterus - cervix								
number examined					6	2		9
Vagina								
number examined					6	2		9

Table 4 Incidence All Microscopic Findings

SEX:	MALE				FEMALE			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Vagina								
Epithelial mucification					3	2		7
Clitoral Glands								
number examined					5			5
Cystic duct, inspissated contents					5			5
Pituitary Gland								
number examined	5			5	5			5
Cyst(s)	0			1	1			0
Thyroid Glands								
number examined	5			5	5			5
Follicular hypertrophy/ hyperplasia, diffuse	2			0	0			0
Parathyroid Glands								
number examined	5			5	5			5
Adrenal Glands								
number examined	5	5	5	5	5	1		5
Extracapsular nodule	0	0	0	1	0	0		1
Vacuolation, multifocal in z. fasiculata	2	2	1	4	0	0		0
Hypertrophy, cortical diffuse	0	0	0	0	0	1		0
Spleen								
number examined	5			5	5			5
Hemopoietic foci, primarily erythroid	5			5	5			5
Hemosiderin pigment	0			1	2			2

Table 4 Incidence All Microscopic Findings

SEX:	*MALE*				*FEMALE*			
DOSE GROUP:	1	2	3	4	1	2	3	4
number of animals	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Bone Marrow - sternal								
number examined	5			5	5			5
Thymus								
number examined	5	5	5	5	5	5	5	5
Lymphoid atrophy - involution	1	0	1	2	4	0	1	3
Mesenteric Lymph Node								
number examined	5			5	5			5
Pigment, yellow-brown	0			0	2			3
Mandibular Lymph Nodes								
number examined	5			5	4			5
Congestion/ erythrophagocytosis	0			0	2			1
Plasmacytosis	1			1	1			0
Lymphoid hyperplasia	2			1	1			0
Skin								
number examined						1		
Telogen (resting) phase follicles						1		
Bone - sternum								
number examined	5			5	5			5
Bone - other sites								
number examined	1	1						
Osseous metaplasia, focal	1	1						

Table 5 Individual Animal Microscopic Findings

Codes and symbols in table heading:

m	Males
f	Females

Codes and symbols in animal lines:

p	Planned sacrifice
i	Suspected infertile

Grading system used in finding lines:

0	finding not present
1	minimal
2	slight
3	moderate
4	severe
5	very severe
x	present

Only organs/groups **with findings** are listed in the table

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Table 5 Individual Animal Microscopic Findings

Males
Group 1

	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m
necropsy status	p	p	p	p	p	p	p	p	p	i
Sciatic Nerve										
Myelin fragmentation	1	0		0		0	1			
Lungs										
Alveolar inflammation, lymphocytic	0	2		0		0	0			
Peri- vascular/bronchial, inflammatory cell foci	0	1		0		1	0			
Lymphoid hyperplasia (BALT)	1	1		0		0	0			
Esophagus										
Myodegeneration, focal	0	0		1		0	2			
Liver										
Inflammation, granulocytic/mononuclear	2	1		1		1	1			
Kidneys										
Pelvic dilation	0	0		0	x	0	0			
Hyaline cast(s)	1	0		0	1	0	0			
Tubular basophilia, corticomedullary	1	0		1	0	0	0			
Prostate Gland										
Inflammation, lymphoid	0	0		0		1	0			0
Preputial Glands										
Cystic duct, inspissated contents	2	0		0		0	1			
Thyroid Glands										
Follicular hypertrophy/ hyperplasia, diffuse	0	1		0		2	0			

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Table 5 Individual Animal Microscopic Findings

Males
Group 1

	1 m	2 m	3 m	4 m	5 m	6 m	7 m	8 m	9 m	10 m
necropsy status	p	p	p	p	p	p	p	p	p	i
Adrenal Glands										
Vacuolation, multifocal in z. fasiculata	1	1		0		0	0			
Spleen										
Hemopoietic foci, primarily erythroid	2	2		1		2	2			
Thymus										
Lymphoid atrophy - involution	0	1		0		0	0			
Mandibular Lymph Nodes										
Plasmacytosis	2	0		0		0	0			
Lymphoid hyperplasia	2	2		0		0	0			
Bone - other sites										
Osseous metaplasia, focal						2				

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Table 5 Individual Animal Microscopic Findings

Males
Group 2

	11 m	12 m	13 m	14 m	15 m	16 m	17 m	18 m	19 m	20 m
necropsy status	i	p	p	p	i	p	p	p	p	i
Lungs										
Lymphoid hyperplasia (BALT)		0	0	1		0	0			
Osseous metaplasia		1	0	0		0	0			
Liver										
Inflammation, granulocytic/mononuclear		2	2	2		2	1			
Kidneys										
Inflammation, lymphoid		0	0	0		0	2			
Tubular basophilia, outer stripe medulla, diffuse		0	0	0		0	3			
Adrenal Glands										
Vacuolation, multifocal in z. fasiculata		1	0	1		0	0			
Bone - other sites										
Osseous metaplasia, focal					2					

Test item : Dytek® DCH-99
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Table 5 Individual Animal Microscopic Findings

Males
Group 3

	21 m	22 m	23 m	24 m	25 m	26 m	27 m	28 m	29 m	30 m
necropsy status	p	p	p	p	p	p	p	p	p	p
Lungs										
Alveolar macrophage foci	1	0	0	0	0					
Alveolar inflammation, lymphocytic	0	0	0	0	1					
Osseous metaplasia	0	2	0	0	0					
Liver										
Inflammation, granulocytic/mononuclear	1	1	2	1	1					
Hematopoietic cell foci	0	1	0	0	0					
Kidneys										
Inflammation, lymphoid	0	0	0	0	1					
Tubular basophilia, corticomedullary	0	0	0	0	1					
Adrenal Glands										
Vacuolation, multifocal in z. fasiculata	2	0	0	0	0					
Thymus										
Lymphoid atrophy - involution	0	0	2	0	0					

Table 5 Individual Animal Microscopic Findings

Males
Group 4

	31 m	32 m	33 m	34 m	35 m	36 m	37 m	38 m	39 m	40 m
necropsy status	p	p	i	p	i	p	i	p	i	p
Sciatic Nerve										
Myelin fragmentation	0	0		1	1	1				
Lungs										
Alveolar macrophage foci	0	0		0	0	2				
Alveolar inflammation, lymphocytic	1	1		0	1	1				
Peri- vascular/bronchial, inflammatory cell foci	0	0		0	1	0				
Liver										
Inflammation, granulocytic/mononuclear	1	1	2	1	1	1				0
Hepatocellular vacuolation	2	0	1	0	1	1				0
Pancreas										
Exocrine atrophy, focal	0	0		0	1	0				
Kidneys										
Hyaline cast(s)	0	0		1	0	0				
Tubular basophilia, corticomedullary	0	1		1	0	0				
Seminal Vesicles										
Acinar atrophy, diffuse	0	0	0	0	0	0	0		2	
Coagulating Glands										
Acinar atrophy, diffuse	0	0	0	0	0	0	0		2	
Pituitary Gland										
Cyst(s)	0	0		0	x	0				

Test item : Dytek® DCH-99
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Table 5 Individual Animal Microscopic Findings

Males
Group 4

	31 m	32 m	33 m	34 m	35 m	36 m	37 m	38 m	39 m	40 m
necropsy status	p	p	i	p	i	p	i	p	i	p
Adrenal Glands										
Extracapsular nodule	0	0		x	0	0				
Vacuolation, multifocal in z. fasiculata	2	2		1	0	2				
Spleen										
Hemopoietic foci, primarily erythroid	2	3		2	2	2				
Hemosiderin pigment	0	1		0	0	0				
Thymus										
Lymphoid atrophy - involution	2	0		0	2	0				
Mandibular Lymph Nodes										
Plasmacytosis	0	3		0	0	0				
Lymphoid hyperplasia	0	0		2	0	0				

Test item : Dytek® DCH-99
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Table 5 Individual Animal Microscopic Findings

Females
Group 1

	41 f	42 f	43 f	44 f	45 f	46 f	47 f	48 f	49 f	50 f
necropsy status	p	p	p	p	p	p	p	p	p	i
Spinal Cord - lumbar										
Axonal swelling, focal		1		0	0		1	0		
Lungs										
Alveolar macrophage foci		2		0	0		0	0		
Alveolar inflammation, lymphocytic		1		0	0		0	0		
Esophagus										
Myodegeneration, focal		2		0	2		0	0		
Stomach										
Dilated gastric pits		0		0	0		1	0		
Liver										
Inflammation, granulocytic/mononuclear		1		0	1		2	1		
Hematopoietic cell foci		2		0	0		0	0		
Kidneys										
Inflammation, lymphoid		0		0	0		0	1		
Tubular basophilia, corticomedullary		0		0	0		1	0		
Uterus										
Implantation site(s)		x		x	x		x	x		0
Estrus epithelium		0		0	0		0	0		x
Vagina										
Epithelial mucification		1		1	2		0	0		0

Test item : Dytek® DCH-99 NOTOX no. : 479003
Test System : Combined Repro/Tox Screening Test by Gavage in Rats Propath no. : 07014
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Table 5 Individual Animal Microscopic Findings

Females
Group 1

	41 f	42 f	43 f	44 f	45 f	46 f	47 f	48 f	49 f	50 f
necropsy status	p	p	p	p	p	p	p	p	p	i
Clitoral Glands										
Cystic duct, inspissated contents		1		2	3		1	3		
Pituitary Gland										
Cyst(s)		0		0	0		x	0		
Spleen										
Hemopoietic foci, primarily erythroid		3		2	2		2	2		
Hemosiderin pigment		1		1	0		0	0		
Thymus										
Lymphoid atrophy - involution		3		1	2		0	2		
Mesenteric Lymph Node										
Pigment, yellow-brown		1		0	1		0	0		
Mandibular Lymph Nodes										
Congestion/ erythrophagocytosis		3		0	0		2	-		
Plasmacytosis		0		0	0		2	-		
Lymphoid hyperplasia		0		0	0		2	-		

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

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Table 5 Individual Animal Microscopic Findings

Females
Group 2

	51 f	52 f	53 f	54 f	55 f	56 f	57 f	58 f	59 f	60 f
necropsy status	i	p	p	p	i	p	p	p	p	i
Lungs										
Alveolar inflammation, lymphocytic		0	0	0				0	1	
Osseous metaplasia		0	1	0				0	0	
Liver										
Inflammation, granulocytic/mononuclear		1	1	1				1	0	
Kidneys										
Hyaline cast(s)		1	0	0				0	2	
Inflammation, lymphoid		0	1	0				1	0	
Tubular basophilia, corticomedullary		1	0	0				1	2	
Uterus										
Implantation site(s)	0				0					x
Inflammation, granulocytic/lymphocytic	0				0					2
Deciduoma	0				x					0
Vagina										
Epithelial mucification	-				4					4
Adrenal Glands										
Hypertrophy, cortical diffuse			2							
Skin										
Telogen (resting) phase follicles									x	

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

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Table 5 Individual Animal Microscopic Findings

Females
Group 3

	61 f	62 f	63 f	64 f	65 f	66 f	67 f	68 f	69 f	70 f
necropsy status	p	p	p	p	p	p	p	p	p	p
Lungs										
Alveolar inflammation, lymphocytic		1	0	0		0				0
Liver										
Hepatodiaphragmatic nodule		0	0	0		x				0
Inflammation, granulocytic/mononuclear		0	0	1		1				0
Hematopoietic cell foci		0	1	0		0				0
Thymus										
Lymphoid atrophy - involution		0	0	0		0				1

Test item : Dytek® DCH-99 NOTOX no. : 479003
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Table 5 Individual Animal Microscopic Findings

Females
Group 4

	71 f	72 f	73 f	74 f	75 f	76 f	77 f	78 f	79 f	80 f
necropsy status	p	p	i	p	i	p	i	p	i	p
Heart										
Inflammation, lymphoid	0	1		0				0		0
Myofiber necrosis	0	0		0				0		1
Lungs										
Alveolar macrophage foci	2	2		3				3		2
Alveolar inflammation, lymphocytic	1	3		2				3		2
Stomach										
Dilated gastric pits	0	0		2				0		1
Liver										
Inflammation, granulocytic/mononuclear	0	1		0				1		1
Hepatocellular vacuolation	0	0		2				1		1
Hematopoietic cell foci	0	0		1				0		0
Kidneys										
Hyaline cast(s)	0	1		0				0		0
Tubular basophilia, corticomedullary	1	1		0				0		1
Uterus										
Implantation site(s)	x	x	0	x	0		0	x	x	x
Inflammation, granulocytic/lymphocytic	0	0	0	0	1		0	0	0	0
Vagina										
Epithelial mucification	0	0	2	2	1		3	3	3	1

Test item : Dytek® DCH-99 NOTOX no. : 479003
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Table 5 Individual Animal Microscopic Findings

Females
Group 4

	71 f	72 f	73 f	74 f	75 f	76 f	77 f	78 f	79 f	80 f
necropsy status	p	p	i	p	i	p	i	p	i	p
Clitoral Glands										
Cystic duct, inspissated contents	2	3		3				1		3
Adrenal Glands										
Extracapsular nodule	x	0		0				0		0
Spleen										
Hemopoietic foci, primarily erythroid	1	1		2				2		2
Hemosiderin pigment	0	1		0				1		0
Thymus										
Lymphoid atrophy - involution	2	3		2				0		0
Mesenteric Lymph Node										
Pigment, yellow-brown	0	1		0				1		1
Mandibular Lymph Nodes										
Congestion/ erythrophagocytosis	3	0		0				0		0

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

NOTOX no. : 479003
Propath no. : 07014
Date : 23.May.2007

Table 6 Animal Data List

Males

ANIMAL NUMBER	SEX M/F	FINAL STATE	TEST DAYS	FIRST DAY	LAST DAY	DATE NECROPSY
DOSE GROUP 1						
1	m	p	31	08/01/07	07/02/07	08/02/07
2	m	p	31	08/01/07	07/02/07	08/02/07
3	m	p	31	08/01/07	07/02/07	08/02/07
4	m	p	31	08/01/07	07/02/07	08/02/07
5	m	p	31	08/01/07	07/02/07	08/02/07
6	m	p	31	08/01/07	07/02/07	08/02/07
7	m	p	31	08/01/07	07/02/07	08/02/07
8	m	p	31	08/01/07	07/02/07	08/02/07
9	m	p	31	08/01/07	07/02/07	08/02/07
10	m	i	31	08/01/07	07/02/07	08/02/07
DOSE GROUP 2						
11	m	i	31	08/01/07	07/02/07	08/02/07
12	m	p	31	08/01/07	07/02/07	08/02/07
13	m	p	31	08/01/07	07/02/07	08/02/07
14	m	p	31	08/01/07	07/02/07	08/02/07
15	m	i	31	08/01/07	07/02/07	08/02/07
16	m	p	31	08/01/07	07/02/07	08/02/07
17	m	p	31	08/01/07	07/02/07	08/02/07
18	m	p	31	08/01/07	07/02/07	08/02/07
19	m	p	31	08/01/07	07/02/07	08/02/07
20	m	i	31	08/01/07	07/02/07	08/02/07
DOSE GROUP 3						
21	m	p	31	08/01/07	07/02/07	08/02/07
22	m	p	31	08/01/07	07/02/07	08/02/07
23	m	p	31	08/01/07	07/02/07	08/02/07
24	m	p	31	08/01/07	07/02/07	08/02/07
25	m	p	31	08/01/07	07/02/07	08/02/07
26	m	p	31	08/01/07	07/02/07	08/02/07
27	m	p	31	08/01/07	07/02/07	08/02/07
28	m	p	31	08/01/07	07/02/07	08/02/07
29	m	p	31	08/01/07	07/02/07	08/02/07
30	m	p	31	08/01/07	07/02/07	08/02/07
DOSE GROUP 4						
31	m	p	31	08/01/07	07/02/07	08/02/07
32	m	p	31	08/01/07	07/02/07	08/02/07
33	m	i	31	08/01/07	07/02/07	08/02/07
34	m	p	31	08/01/07	07/02/07	08/02/07
35	m	i	31	08/01/07	07/02/07	08/02/07
36	m	p	31	08/01/07	07/02/07	08/02/07
37	m	i	31	08/01/07	07/02/07	08/02/07
38	m	p	31	08/01/07	07/02/07	08/02/07
39	m	i	31	08/01/07	07/02/07	08/02/07
40	m	p	31	08/01/07	07/02/07	08/02/07

Table 6 Animal Data List

Females

ANIMAL NUMBER	SEX M/F	FINAL STATE	TEST DAYS	FIRST DAY	LAST DAY	DATE NECROPSY
DOSE GROUP 1						
41	f	p	45	08/01/07	21/02/07	22/02/07
42	f	p	44	08/01/07	20/02/07	21/02/07
43	f	p	42	08/01/07	18/02/07	19/02/07
44	f	p	43	08/01/07	19/02/07	20/02/07
45	f	p	43	08/01/07	19/02/07	20/02/07
46	f	p	42	08/01/07	18/02/07	19/02/07
47	f	p	43	08/01/07	19/02/07	20/02/07
48	f	p	43	08/01/07	19/02/07	20/02/07
49	f	p	44	08/01/07	20/02/07	21/02/07
50	f	i	45	08/01/07	21/02/07	21/02/07
DOSE GROUP 2						
51	f	i	45	08/01/07	21/02/07	21/02/07
52	f	p	45	08/01/07	21/02/07	22/02/07
53	f	p	42	08/01/07	18/02/07	19/02/07
54	f	p	43	08/01/07	19/02/07	20/02/07
55	f	i	45	08/01/07	21/02/07	21/02/07
56	f	p	45	08/01/07	21/02/07	22/02/07
57	f	p	45	08/01/07	21/02/07	22/02/07
58	f	p	42	08/01/07	18/02/07	19/02/07
59	f	p	43	08/01/07	19/02/07	20/02/07
60	f	i	39	08/01/07	15/02/07	15/02/07
DOSE GROUP 3						
61	f	p	45	08/01/07	21/02/07	22/02/07
62	f	p	42	08/01/07	18/02/07	19/02/07
63	f	p	44	08/01/07	20/02/07	21/02/07
64	f	p	42	08/01/07	18/02/07	19/02/07
65	f	p	42	08/01/07	18/02/07	19/02/07
66	f	p	44	08/01/07	20/02/07	21/02/07
67	f	p	44	08/01/07	20/02/07	21/02/07
68	f	p	44	08/01/07	20/02/07	21/02/07
69	f	p	42	08/01/07	18/02/07	19/02/07
70	f	p	43	08/01/07	19/02/07	20/02/07
DOSE GROUP 4						
71	f	p	44	08/01/07	20/02/07	21/02/07
72	f	p	43	08/01/07	19/02/07	20/02/07
73	f	i	45	08/01/07	21/02/07	21/02/07
74	f	p	44	08/01/07	20/02/07	21/02/07
75	f	i	45	08/01/07	21/02/07	21/02/07
76	f	p	44	08/01/07	20/02/07	21/02/07
77	f	i	45	08/01/07	21/02/07	21/02/07
78	f	p	43	08/01/07	19/02/07	20/02/07
79	f	i	41	08/01/07	17/02/07	17/02/07
80	f	p	43	08/01/07	19/02/07	20/02/07

Table 7 Individual Animal Data Records

Animal No: 1
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Kidney/1	Hyaline cast(s) (minimal) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (slight)
Lungs	Lymphoid hyperplasia (BALT) (minimal)
Mandibular Lymph Node/1	Plasmacytosis (slight)
Mandibular Lymph Node/2	Lymphoid hyperplasia (slight)
Preputial Gland/1	Cystic duct, inspissated contents (slight)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)

Table 7 Individual Animal Data Records

Animal No: 1
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/2, Prostate Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 2

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar inflammation, lymphocytic (slight) Peri- vascular/bronchial, inflammatory cell foci (minimal) Lymphoid hyperplasia (BALT) (minimal)
Mandibular Lymph Node/1	Lymphoid hyperplasia (slight)

Table 7 Individual Animal Data Records

Animal No: 2
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

Mandibular Lymph Node/2	Lymphoid hyperplasia (slight)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thymus	Lymphoid atrophy - involution (minimal)
Thyroid Gland/1	Follicular hypertrophy/hyperplasia, diffuse (minimal)
Thyroid Gland/2	Follicular hypertrophy/hyperplasia, diffuse (minimal)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Trachea, Urinary Bladder.

Animal No: 3

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 4

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Esophagus	Myodegeneration, focal (minimal)
Kidney/1	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Table 7 Individual Animal Data Records

Animal No: 5
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Kidneys	right side Pelvic dilation
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Kidney/1	Pelvic dilation present (correlates to GROSS finding) Hyaline cast(s) (minimal)

Animal No: 6

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Bone	tail apex Bent
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Bone - other sites	Osseous metaplasia, focal (slight) (correlates to GROSS finding)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Peri- vascular/bronchial, inflammatory cell foci (minimal)

Table 7 Individual Animal Data Records

Animal No: 6
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

Prostate Gland	Inflammation, lymphoid (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thyroid Gland/1	Follicular hypertrophy/hyperplasia, diffuse (slight)
Thyroid Gland/2	Follicular hypertrophy/hyperplasia, diffuse (slight)

Number of Sections less than protocol for Parathyroid Gland/1 (0).

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Trachea, Urinary Bladder.

Animal No: 7

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 7
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS

Esophagus	Myodegeneration, focal (slight)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Preputial Gland/1	Cystic duct, inspissated contents (minimal)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)

Number of Sections less than protocol for Coagulating Gland/1 (0).

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/2, Prostate Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 8

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 8
SEX: Male
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 9

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 10

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/1, Seminal Vesicle/2, Testes/1, Testes/2.

Table 7 Individual Animal Data Records

Animal No: 41
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 22/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 42

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

Mandibular lymph nodes: right side Discolouration DARK RED

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1: Cystic duct, inspissated contents (minimal)

Esophagus: Myodegeneration, focal (slight)

Liver: Inflammation, granulocytic/mononuclear (minimal)
Hematopoietic cell foci (slight)

Lungs: Alveolar macrophage foci (slight)
Alveolar inflammation, lymphocytic (minimal)

Table 7 Individual Animal Data Records

Animal No: 42
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

Mandibular Lymph Node/1	Congestion/erythrophagocytosis (moderate) (correlates to GROSS finding)
Mesenteric Lymph Node	Pigment, yellow-brown (minimal)
Spinal Cord - lumbar	Axonal swelling, focal (minimal)
Spleen	Hemopoietic foci, primarily erythroid (moderate) Hemosiderin pigment (minimal)
Thymus	Lymphoid atrophy - involution (moderate)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (minimal)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Clitoral Gland/2, Colon, Duodenum, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/2, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Animal No: 43

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 43
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 44

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

No findings noted

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (slight)
Spleen	Hemopoietic foci, primarily erythroid (slight) Hemosiderin pigment (minimal)
Thymus	Lymphoid atrophy - involution (minimal)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Clitoral Gland/2, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Liver, Lungs, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Table 7 Individual Animal Data Records

Animal No: 45
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

No findings noted

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (moderate)
Clitoral Gland/2	Cystic duct, inspissated contents (moderate)
Esophagus	Myodegeneration, focal (slight)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Mesenteric Lymph Node	Pigment, yellow-brown (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thymus	Lymphoid atrophy - involution (slight)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (slight)

Number of Sections less than protocol for Mandibular Lymph Node/1 (0), Parathyroid Gland/1 (0).

Table 7 Individual Animal Data Records

Animal No: 45
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Lungs, Mandibular Lymph Node/2, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Animal No: 46

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 47

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

Mandibular lymph nodes — both sides Discolouration DARK RED

Table 7 Individual Animal Data Records

Animal No: 47
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS
(continued)

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (minimal)
Kidney/1	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (slight)
Mandibular Lymph Node/1	Congestion/erythrophagocytosis (slight) (correlates to GROSS finding)
Mandibular Lymph Node/2	Plasmacytosis (slight) Lymphoid hyperplasia (slight)
Pituitary Gland	Cyst(s) present
Spinal Cord - lumbar	Axonal swelling, focal (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Stomach	Dilated gastric pits (minimal)
Uterus	Implantation site(s) present

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Clitoral Gland/2, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix, Vagina.

Table 7 Individual Animal Data Records

Animal No: 48
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

No findings noted

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (slight)
Clitoral Gland/2	Cystic duct, inspissated contents (moderate)
Kidney/1	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thymus	Lymphoid atrophy - involution (slight)
Uterus	Implantation site(s) present

Number of Sections less than protocol for Mandibular Lymph Node/1 (0), Mandibular Lymph Node/2 (0).

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Lungs, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix, Vagina.

Table 7 Individual Animal Data Records

Animal No: 49
SEX: Female
DOSE GROUP: Group 1, 0 mg/kg/day Control

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 50

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Uterus Estrus epithelium present

No abnormalities found in: Ovary/1, Ovary/2, Uterus - cervix, Vagina.

Table 7 Individual Animal Data Records

Animal No: 11
SEX: Male
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/1, Seminal Vesicle/2, Testes/1, Testes/2.

Animal No: 12

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Liver	Inflammation, granulocytic/mononuclear (slight)
Lungs	Osseous metaplasia (minimal)

No abnormalities found in: Kidney/1, Kidney/2, Thymus.

Table 7 Individual Animal Data Records

Animal No: 13
SEX: Male
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (slight)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/1, Kidney/2, Lungs, Thymus.

Animal No: 14

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Liver	Inflammation, granulocytic/mononuclear (slight)
Lungs	Lymphoid hyperplasia (BALT) (minimal)

No abnormalities found in: Adrenal Gland/2, Kidney/1, Kidney/2, Thymus.

Table 7 Individual Animal Data Records

Animal No: 15
SEX: Male
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

Bone — tail apex Bent

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Bone - other sites — Osseous metaplasia, focal (slight) (correlates to GROSS finding)

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/1, Seminal Vesicle/2, Testes/1, Testes/2.

Animal No: 16

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver — Inflammation, granulocytic/mononuclear (slight)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/1, Kidney/2, Lungs, Thymus.

Table 7 Individual Animal Data Records

Animal No: 17
SEX: Male
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Inflammation, lymphoid (slight) Tubular basophilia, outer stripe medulla, diffuse (moderate)
Kidney/2	Inflammation, lymphoid (slight) Tubular basophilia, outer stripe medulla, diffuse (moderate)
Liver	Inflammation, granulocytic/mononuclear (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Lungs, Thymus.

Animal No: 18

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Table 7 Individual Animal Data Records

Animal No: 19
SEX: Male
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 20

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

Seminal vesicles right side Reduced in size

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Seminal Vesicle/1 Small organ, normal histology (correlates to GROSS finding)

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/2, Testes/1, Testes/2.

Table 7 Individual Animal Data Records

Animal No: 51
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

Cervix — Enlarged

Uterus — Contains fluid
Enlarged

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Uterus — Extreme dilation, endothelium with focal areas of squamous metaplasia (correlates to GROSS finding)

Number of Sections less than protocol for Uterus - cervix (0), Vagina (0).

No abnormalities found in: Ovary/1, Ovary/2.

Animal No: 52

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 22/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 52
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MICROSCOPIC FINDINGS

Kidney/1	Hyaline cast(s) (minimal) Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
	No abnormalities found in: Kidney/2, Lungs, Thymus.

Animal No: 53

MACROSCOPIC FINDINGS

	days of treatment : 42 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 18/02/07 date of necropsy : 19/02/07
Adrenal glands	both sides Enlarged
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Adrenal Gland/1	Hypertrophy, cortical diffuse (slight) (correlates to GROSS finding)
Adrenal Gland/2	Hypertrophy, cortical diffuse (slight)
Kidney/1	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Osseous metaplasia (minimal)
	No abnormalities found in: Kidney/2, Thymus.

Table 7 Individual Animal Data Records

Animal No: 54
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver — Inflammation, granulocytic/mononuclear (minimal)

No abnormalities found in: Kidney/1, Kidney/2, Lungs, Thymus.

Animal No: 55

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Uterus — Deciduoma present

Vagina — Epithelial mucification (severe)

No abnormalities found in: Ovary/1, Ovary/2, Uterus - cervix.

Table 7 Individual Animal Data Records

Animal No: 56
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 22/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 57

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 22/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 58

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 58
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MICROSCOPIC FINDINGS

Kidney/1	Tubular basophilia, corticomedullary (minimal)
Kidney/2	Inflammation, lymphoid (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
	No abnormalities found in: Lungs, Thymus.

Animal No: 59

MACROSCOPIC FINDINGS

	days of treatment : 43 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 19/02/07 date of necropsy : 20/02/07
Skin	right side, hindleg Alopecia
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Kidney/1	Hyaline cast(s) (slight)
Kidney/2	Hyaline cast(s) (slight) Tubular basophilia, corticomedullary (slight)
Lungs	Alveolar inflammation, lymphocytic (minimal)
Skin	Telogen (resting) phase follicles present (correlates to GROSS finding)
	No abnormalities found in: Liver, Thymus.

Table 7 Individual Animal Data Records

Animal No: 60
SEX: Female
DOSE GROUP: Group 2, 50 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 39
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 15/02/07
date of necropsy : 15/02/07

Stomach — contents: Reddish

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Stomach — No correlate to macro

Uterus — Implantation site(s) present
Inflammation, granulocytic/lymphocytic (slight)
Serosanguinous uterine contents

Vagina — Epithelial mucification (severe)

No abnormalities found in: Ovary/1, Ovary/2, Uterus - cervix.

Animal No: 21
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 21
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (slight)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (slight)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar macrophage foci (minimal)
	No abnormalities found in: Kidney/1, Kidney/2, Thymus.

Animal No: 22

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (minimal) Hematopoietic cell foci (minimal)
Lungs	Osseous metaplasia (slight)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/1, Kidney/2, Thymus.

Table 7 Individual Animal Data Records

Animal No: 23
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (slight)
Thymus	Lymphoid atrophy - involution (slight)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/1, Kidney/2, Lungs.

Animal No: 24

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/1, Kidney/2, Lungs, Thymus.

Table 7 Individual Animal Data Records

Animal No: 25
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Kidney/1	Inflammation, lymphoid (minimal) Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar inflammation, lymphocytic (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Kidney/2, Thymus.

Animal No: 26

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Table 7 Individual Animal Data Records

Animal No: 27
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 28

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 29

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 29
SEX: Male
DOSE GROUP: Group 3, 150 mg/kg/day

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 30

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

Seminal vesicles left side Reduced in size

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Seminal Vesicle/1 No correlate to macro

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Seminal Vesicle/2.

Animal No: 61
SEX: Female

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 22/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Table 7 Individual Animal Data Records

Animal No: 62
SEX: Female
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

MICROSCOPIC FINDINGS

Lungs — Alveolar inflammation, lymphocytic (minimal)

No abnormalities found in: Kidney/1, Kidney/2, Liver, Thymus.

Animal No: 63

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver — Hematopoietic cell foci (minimal)

No abnormalities found in: Kidney/1, Kidney/2, Lungs, Thymus.

Table 7 Individual Animal Data Records

Animal No: 64
SEX: Female
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

MICROSCOPIC FINDINGS

Liver Inflammation, granulocytic/mononuclear (minimal)

No abnormalities found in: Kidney/1, Kidney/2, Lungs, Thymus.

Animal No: 65

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 66

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

Table 7 Individual Animal Data Records

Animal No: 66
SEX: Female
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

Liver	right lateral lobe Diaphragmatic hernia
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Liver	Hepatodiaphragmatic nodule present (correlates to GROSS finding) Inflammation, granulocytic/mononuclear (minimal)
	No abnormalities found in: Kidney/1, Kidney/2, Lungs, Thymus.

Animal No: 67

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 68

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

Table 7 Individual Animal Data Records

Animal No: 68
SEX: Female
DOSE GROUP: Group 3, 150 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 69

MACROSCOPIC FINDINGS

days of treatment : 42
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 18/02/07
date of necropsy : 19/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 70

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 70
SEX: Female
DOSE GROUP: Group 3, 150 mg/kg/day

MICROSCOPIC FINDINGS

Thymus	Lymphoid atrophy - involution (minimal) Ectopic parathyroid tissue
	No abnormalities found in: Kidney/1, Kidney/2, Liver, Lungs.

Animal No: 31
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Liver	Discolouration PALE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (slight)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal) Hepatocellular vacuolation (slight) (correlates to GROSS finding)
Lungs	Alveolar inflammation, lymphocytic (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thymus	Lymphoid atrophy - involution (slight)

Table 7 Individual Animal Data Records

Animal No: 31
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 32

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (slight)
Kidney/1	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar inflammation, lymphocytic (minimal)

Table 7 Individual Animal Data Records

Animal No: 32
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

Mandibular Lymph Node/1	Plasmacytosis (moderate)
Spleen	Hemopoietic foci, primarily erythroid (moderate) Hemosiderin pigment (minimal)
	No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Sciatic Nerve, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 33

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : suspected infertile date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Liver	Discolouration PALE
	No abnormalities were found in any of the other tissues examined

Table 7 Individual Animal Data Records

Animal No: 33
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (slight) Hepatocellular vacuolation (minimal) (correlates to GROSS finding)
	No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/1, Seminal Vesicle/2, Testes/1, Testes/2.

Animal No: 34

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

Adrenal Gland/1	Extracapsular nodule present Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (minimal)
Kidney/1	Hyaline cast(s) (minimal) Tubular basophilia, corticomedullary (minimal)
Kidney/2	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Mandibular Lymph Node/1	Lymphoid hyperplasia (slight)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)

Table 7 Individual Animal Data Records

Animal No: 34
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/1, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Lungs, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 35

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

Liver	Discolouration PALE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Liver	Inflammation, granulocytic/mononuclear (minimal) (correlates to GROSS finding) Hepatocellular vacuolation (minimal)
Lungs	Alveolar inflammation, lymphocytic (minimal) Peri- vascular/bronchial, inflammatory cell foci (minimal)
Pancreas	Exocrine atrophy, focal (minimal)

Table 7 Individual Animal Data Records

Animal No: 35
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

Pituitary Gland	Cyst(s) present
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Thymus	Lymphoid atrophy - involution (slight)
	Number of Sections less than protocol for Coagulating Gland/1 (0).
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 36

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Liver	Discolouration PALE
	No abnormalities were found in any of the other tissues examined

Table 7 Individual Animal Data Records

Animal No: 36
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS

Adrenal Gland/1	Vacuolation, multifocal in z. fasiculata (minimal)
Adrenal Gland/2	Vacuolation, multifocal in z. fasiculata (slight)
Liver	Inflammation, granulocytic/mononuclear (minimal) Hepatocellular vacuolation (minimal) (correlates to GROSS finding)
Lungs	Alveolar macrophage foci (slight) Alveolar inflammation, lymphocytic (minimal)
Sciatic Nerve	Myelin fragmentation (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight)

Number of Sections less than protocol for Coagulating Gland/1 (0).

No abnormalities found in: Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Coagulating Gland/2, Colon, Duodenum, Epididymis/1, Epididymis/2, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Preputial Gland/1, Preputial Gland/2, Prostate Gland, Rectum, Seminal Vesicle/1, Seminal Vesicle/2, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Testes/1, Testes/2, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder.

Animal No: 37

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

Table 7 Individual Animal Data Records

Animal No: 37
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

No findings noted

MICROSCOPIC FINDINGS

No abnormality detected

No abnormalities found in: Coagulating Gland/1, Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/1, Seminal Vesicle/2, Testes/1, Testes/2.

Animal No: 38

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Animal No: 39

MACROSCOPIC FINDINGS

days of treatment : 31
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 07/02/07
date of necropsy : 08/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 39
SEX: Male
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS

Coagulating Gland/1	Acinar atrophy, diffuse (slight)
Seminal Vesicle/1	Acinar atrophy, diffuse (slight)
	No abnormalities found in: Coagulating Gland/2, Epididymis/1, Epididymis/2, Prostate Gland, Seminal Vesicle/2, Testes/1, Testes/2.

Animal No: 40

MACROSCOPIC FINDINGS

	days of treatment : 31 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 07/02/07 date of necropsy : 08/02/07
Liver	Discolouration PALE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Liver	No correlate to macro

Animal No: 71
SEX: Female

MACROSCOPIC FINDINGS

	days of treatment : 44 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 20/02/07 date of necropsy : 21/02/07
Mandibular lymph nodes	right side Discolouration DARK RED

Table 7 Individual Animal Data Records

Animal No: 71
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Adrenal Gland/1	Extracapsular nodule present
Aorta	Base of heart
Clitoral Gland/1	Cystic duct, inspissated contents (slight)
Kidney/1	Tubular basophilia, corticomedullary (minimal)
Lungs	Alveolar macrophage foci (slight) Alveolar inflammation, lymphocytic (minimal)
Mandibular Lymph Node/1	Congestion/erythrophagocytosis (moderate) (correlates to GROSS finding)
Spleen	Hemopoietic foci, primarily erythroid (minimal)
Thymus	Lymphoid atrophy - involution (slight)
Uterus	Implantation site(s) present

No abnormalities found in: Adrenal Gland/2, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Clitoral Gland/2, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/2, Liver, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix, Vagina.

Table 7 Individual Animal Data Records

Animal No: 72
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS

	days of treatment : 43 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 19/02/07 date of necropsy : 20/02/07
Lungs	Focus/foci MANY, GRAY-WHITE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (moderate)
Clitoral Gland/2	Cystic duct, inspissated contents (moderate)
Heart	Inflammation, lymphoid (minimal)
Kidney/1	Hyaline cast(s) (minimal) Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal)
Lungs	Alveolar macrophage foci (slight) (correlates to GROSS finding) Alveolar inflammation, lymphocytic (moderate) (correlates to GROSS finding)
Mesenteric Lymph Node	Pigment, yellow-brown (minimal)
Spleen	Hemopoietic foci, primarily erythroid (minimal) Hemosiderin pigment (minimal)
Thymus	Lymphoid atrophy - involution (moderate)
Uterus	Implantation site(s) present

Table 7 Individual Animal Data Records

Animal No: 72
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Ileum, Jejunum, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix, Vagina.

Animal No: 73

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Vagina — Epithelial mucification (slight)

No abnormalities found in: Ovary/1, Ovary/2, Uterus, Uterus - cervix.

Animal No: 74

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

Table 7 Individual Animal Data Records

Animal No: 74
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS
(continued)

Lungs	Focus/foci MANY, GRAY-WHITE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (moderate)
Clitoral Gland/2	Cystic duct, inspissated contents (slight)
Liver	Hepatocellular vacuolation (slight) Hematopoietic cell foci (minimal)
Lungs	Alveolar macrophage foci (moderate) Alveolar inflammation, lymphocytic (slight)
Spleen	Hemopoietic foci, primarily erythroid (slight)
Stomach	Dilated gastric pits (slight)
Thymus	Lymphoid atrophy - involution (slight)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (slight)
	No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Mesenteric Lymph Node, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Table 7 Individual Animal Data Records

Animal No: 75
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Uterus — Inflammation, granulocytic/lymphocytic (minimal)

Vagina — Epithelial mucification (minimal)

Number of Sections less than protocol for Ovary/1 (0).

No abnormalities found in: Ovary/2, Uterus - cervix.

Animal No: 76

MACROSCOPIC FINDINGS

days of treatment : 44
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 20/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

No tissues taken

Table 7 Individual Animal Data Records

Animal No: 77
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MACROSCOPIC FINDINGS

days of treatment : 45
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 21/02/07
date of necropsy : 21/02/07

No findings noted

MICROSCOPIC FINDINGS

Vagina	Epithelial mucification (moderate)
	No abnormalities found in: Ovary/1, Ovary/2, Uterus, Uterus - cervix.

Animal No: 78

MACROSCOPIC FINDINGS

days of treatment : 43
sacrifice group : planned terminal
necropsy status : planned terminal
date of start of treatment: 08/01/07
date of end of treatment: 19/02/07
date of necropsy : 20/02/07

Lungs	Focus/foci MANY, GRAY-WHITE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal) Hepatocellular vacuolation (minimal)
Lungs	Alveolar macrophage foci (moderate) (correlates to GROSS finding) Alveolar inflammation, lymphocytic (moderate) (correlates to GROSS finding)

Table 7 Individual Animal Data Records

Animal No: 78
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

Mesenteric Lymph Node	Pigment, yellow-brown (minimal)
Spleen	Hemopoietic foci, primarily erythroid (slight) Hemosiderin pigment (minimal)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (moderate)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Clitoral Gland/2, Colon, Duodenum, Esophagus, Heart, Ileum, Jejunum, Kidney/1, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Stomach, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Animal No: 79

MACROSCOPIC FINDINGS

days of treatment : 41
sacrifice group : planned terminal
necropsy status : suspected infertile
date of start of treatment: 08/01/07
date of end of treatment: 17/02/07
date of necropsy : 17/02/07

No findings noted

Table 7 Individual Animal Data Records

Animal No: 79
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS

Uterus	Implantation site(s) present
Vagina	Epithelial mucification (moderate)
	No abnormalities found in: Ovary/1, Ovary/2, Uterus - cervix.

Animal No: 80

MACROSCOPIC FINDINGS

	days of treatment : 43 sacrifice group : planned terminal necropsy status : planned terminal date of start of treatment: 08/01/07 date of end of treatment: 19/02/07 date of necropsy : 20/02/07
Lungs	Focus/foci MANY, GRAY-WHITE
	No abnormalities were found in any of the other tissues examined

MICROSCOPIC FINDINGS

Clitoral Gland/1	Cystic duct, inspissated contents (moderate)
Clitoral Gland/2	Cystic duct, inspissated contents (slight)
Heart	Myofiber necrosis (minimal)
Kidney/1	Tubular basophilia, corticomedullary (minimal)
Liver	Inflammation, granulocytic/mononuclear (minimal) Hepatocellular vacuolation (minimal)
Lungs	Alveolar macrophage foci (slight) (correlates to GROSS finding) Alveolar inflammation, lymphocytic (slight) (correlates to GROSS finding)
Mesenteric Lymph Node	Pigment, yellow-brown (minimal)

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

NOTOX no. : 479003
Propath no. : 07014
Date : 23.May.2007

Table 7 Individual Animal Data Records

Animal No: 80
SEX: Female
DOSE GROUP: Group 4, 500 mg/kg/day

MICROSCOPIC FINDINGS
(continued)

Spleen	Hemopoietic foci, primarily erythroid (slight)
Stomach	Dilated gastric pits (minimal)
Uterus	Implantation site(s) present
Vagina	Epithelial mucification (minimal)

No abnormalities found in: Adrenal Gland/1, Adrenal Gland/2, Aorta, Bone - sternum, Bone Marrow - sternal, Brain, Cecum, Colon, Duodenum, Esophagus, Ileum, Jejunum, Kidney/2, Mandibular Lymph Node/1, Mandibular Lymph Node/2, Ovary/1, Ovary/2, Pancreas, Parathyroid Gland/1, Parathyroid Gland/2, Peyer's Patches (GALT), Pituitary Gland, Rectum, Sciatic Nerve, Spinal Cord - cervical, Spinal Cord - midthoracic, Spinal Cord - lumbar, Thymus, Thyroid Gland/1, Thyroid Gland/2, Trachea, Urinary Bladder, Uterus - cervix.

Test item : Dytek® DCH-99
Test System : Combined Repro/Tox Screening Test by Gavage in Rats
Sponsor : Invista S.a.r.l.

NOTOX no. : 479003
Propath no. : 07014
Date : 23.May.2007

Table 8 Staging of Spermatogenesis

Stage:	I	II - III	IV	V	VI	VII	VIII	IX	X	XI	XII - XIII	XIV	Comments
animal no.													
1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Unilateral minimal Spermatidic giant cells
6	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
31	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
32	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
34	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
35	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
36	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Unilateral minimal tubular atrophy

✓ = Stage present × = Stage missing ? = See comment

I - III: No acrosome IV - VI: Acrosome VII - VIII: Sperm release IX - XI: Round → oval spermatid nucleus XII - XIV: Spermatid head rod-shaped

APPENDIX 5 SUMMARY DOSE RANGE FINDING STUDY

SUMMARY OF DOSE RANGE FINDING STUDY

In order to set the dose levels for the main study (NOTOX Project 479003), a pilot study was performed.

In first instance, groups of 3 females (6-12 weeks old) were dosed at 500 or 1000 mg/kg body weight/day (Groups 1 and 2) for 8 days by oral gavage with a dose volume of 5 ml/kg body weight. Based on the results obtained at these dose levels, it was decided to increase the dose volume, by which the dose concentration was decreased to solve irritation to the stomach. Three naïve animals (8-10 weeks old) were dosed at 500 mg/kg body weight/day (Group 3) for 8 days by oral gavage at a dose volume of 20 ml/kg body weight. Subsequently, three naïve animals were dosed at 1000 mg/kg body weight/day (Group 4) for 8 days by oral gavage at a dose volume of 20 ml/kg body weight.

All animals were housed 3 per cage, identified by ear- and tailmark and allocation was performed at random. If not mentioned otherwise, test system and techniques were identical to those used during the main study.

Data was collected under NOTOX Project 481038.

Planning	Delivery:	15 November 2006
	Start treatment:	24 November 2006 (Groups 1 and 2)
		01 December 2006 (Group 3)
		13 December 2006 (Group 4)
	Terminal procedures:	
		08 December 2006 (Group 3)
		20 December 2006 (Group 4)
Chemical analysis	Not performed during the pilot study.	
Observations	Clinical signs: At least once daily.	
	Mortality: At least twice daily.	
	Body weights: On Days 1, 4 and 8.	
	Food consumption: Over Days 1-4 and 4-8.	
Pathology	No organs were fixed.	
	Terminal body weight, organ weights: kidney and liver.	

RESULTS

<u>500 and 1000 mg/kg, 5 ml/kg</u>
Two females at 500 mg/kg and a dose volume of 5 ml/kg and one female at 1000 mg/kg and a dose volume of 5 ml/kg were killed in extremis on 27 November 2006. These animals showed severe body weight loss, clinical signs and at necropsy stomach abnormalities.

<u>500 mg/kg, 20 ml/kg</u>
Reduced body weight gain and food consumption was observed.

<u>1000 mg/kg, 20 ml/kg</u>
Severe toxicity was observed, which comprised of death and stomach and/or liver abnormalities.

CONCLUSION

Based on these results, the dose levels for the main study will be 50, 150 and 500 mg/kg body weight/day, at a dose volume of 20 ml/kg.